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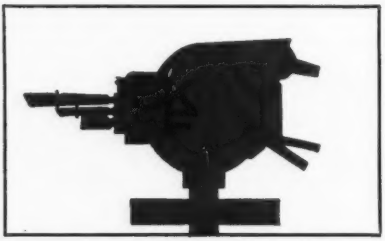

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CORRESPONDENCE

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Cardiac Massage And Drowning

(Consultant, June '61)

Dear Doctor Jude:

How would you eliminate the water in a victim of drowning when applying external cardiac massage? What procedure would you recommend?

—William A. Schmidt, M.D.
Shenandoah, Pa.

Although I do not know of any cases where external cardiac massage has been used in drowning victims, I would think that the water should be eliminated in the same way that it is now being eliminated in the present methods of resuscitation. That is, the patient's head should be placed much lower than the waist and the head turned to one side. Attempt should be made to clear out the mouth and oropharynx very rapidly to insure as good an air passage as possible. With the head turned in this position and lowered, it is hoped that water in the lungs will run out by gravity. Of course, very good ventilation by the mouth-to-mouth technique should be employed concomitantly with external massage.

—James R. Jude, M.D.

Psychiatric Referral

(Consultant, July '61)

Dear Sir:

I can readily agree with Dr. Garrard's opinion that the referring family physician should not expect to play a very active role in the psychiatric treatment of his patient. But should he expect to be kept informed of his patient's progress?

—Mary P. Sterling, M.D.
Philadelphia, Penna.

A breakdown of communication between psychiatrists and referring physicians is apparently one of the major problems creating uncomfortable relationships between them. In my opinion, the referring physician is certainly entitled to a complete report in understandable terminology (excluding only, perhaps, very confidential data that could be very harmful to the patient or the family if it became known) and should receive progress reports from time to time. While I prefer to send written reports, I don't really think it matters if they are made orally.

If, for one reason or another, you do not get some kind of report from the psychiatrist, you should ask for one. He may have forgotten it or, because it is so often true, he may have assumed that you didn't want one. Quite often, perhaps more often than you think, physicians refer patients to a psychiatrist to get them off their hands. When that is not the case, you should tell the psychiatrist you would appreciate it if he would keep you informed about the patient. If you do this, and remind him of your request later, and still don't get a report, I don't know what to suggest, except that you refer your patients elsewhere.

—Robert L. Garrard, M.D.

Fatherhood After Vasectomy?

Dear Sirs:

Recently I was called to court to testify in a paternity disagreement in a divorce case involving a vasectomy. The facts were these: At the age of 36, the husband had a bilateral vasectomy for sterilization purposes. He never returned for sperm counts or ejaculate exam until 3 years later when the trial started. At that time he was found to be sterile by 3 independent ejaculate examinations. His ejaculate then contained no sperm at all. The story was that fourteen months after his vasectomy, his wife had conceived a child. During the three years following his vasectomy, he had no illnesses other than a viral U.R.I. or two. There was nothing in his medical history to indicate an illness which could have caused sterility. The obvious question for the court to decide was (1) was it correct to assume that his present sterility was due to a (the) successful vasectomy? (2) assuming post operative intercourse of 2-4 times per week, when had he become sterile after the vasectomy? (3) could he possibly have been the father of the child conceived 14 months after the vasectomy? (He had fathered 3 other children.)

My questions are: (1) what would be your medical testimony to my above 3 questions in court? (2) is there any report in the literature documenting how soon (either in time or number of intercourses) after a vasectomy the patient becomes sterile (on a large series of cases)? (3) are there any reported cases with photomicrograph proof *of reanastomoses or recanalization of vasectomies with subsequent fertility? (4) are*

there any reports or monographs concerning the process of "recanalization" of the vas deferens following a vasectomy wherein a section of each vas was removed? I have found the literature vague and scanty on this subject (vasectomy, recanalization, post operative infertility).

– MD (Name withheld on request)

When this letter was received, CONSULTANT did not have a contributing Urologist to whom the questions could be referred. However, a literature search was conducted to provide the writer with background information. The following excerpts from the literature may be of interest to CONSULTANT's readers.

The sources consulted were the *Quarterly Cumulative Index Medicus* (1930-1950) and the *Current List of Medical Literature* (Index Medicus) (1950-May 1961).

Question #1 – How soon after a vasectomy does the patient become sterile?

According to the literature, there is no definite answer to this question. Usually the genital tract is free of sperm within a few weeks or at the most within a few months. However, there have been reports that viable sperm have persisted for over a year. As a result of the wide variations found in the literature, sperm counts must be done at regular intervals on all vasectomized patients until no viable sperm are found in the ejaculate. Only then can the patient be considered to be sterile.

Question #2 – Are there any cases, with photomicrographical proof, of recanalization of the vas deferens with subsequent fertility?

There are several reports that discuss cases in which the wife conceived as a result of recanalization of the vas deferens. For example in his article *Anastomosis of the vas deferens* (J.A.M.A. 136:162-63, 1948) O'Conor reported that he sent a questionnaire to the members of the American Urology Association to determine the success of the surgical reanastomosis of the vas. Of 750 replies, 55 reported authentic spontaneous recanalization after resection. In each instance sections of the vas were removed and confirmed by microscopic examination at the time of the original surgery.

When questioned whether they knew of any pregnancies in the female of a husband who had had a vasectomy, 349 urologists (36%) replied yes, 594 (61%), no, and 28, no reply. One hundred and six added comments about infidelity, hearsay pregnancies, etc.

Question #3 – Are there any reports or monographs concerning the process of recanalization of the vas deferens?

Rolnick (*J. Urol.* 9:188-203, 1924) experimented on dogs to determine the power of the vas to regenerate and restore continuity of the lumen. In simple ligation restoration consistently occurred in each dog. With multiple incisions, the lumen remained patent in 3 out of 5 dogs. If the vas is divided or resected for as much as 1.5 to 2 inches, regeneration may well occur provided the sheath of the vas is partially or completely intact; without the sheath, regeneration occurs only in a small percentage of cases. Several other reports also describe recanalization of the vas deferens in animals.

ABO Incompatibility In The Newborn

(Consultant, June 1961)

Sir:

I wonder if Doctor DeCosta could tell us the incidence of erythroblastosis fetalis due to ABO incompatibility, and how often these sensitivities are sufficiently serious to require exchange transfusions.

– G. R. Hugman, M.D.
Gladewater, Texas

A few years ago, we thought that erythroblastosis fetalis was rarely caused by ABO incompatibility because the clinical symptoms are frequently so mild that they escape notice. However, careful laboratory studies now detect the disease in about 2% of all newborn babies, about twice the incidence of erythroblastosis due to Rh incompatibility. In contrast to Rh erythroblastosis, ABO erythroblastosis is usually not serious enough to require treatment. Kernicterus, which may cause brain damage or death, is the only dangerous complication, and it has been estimated to occur in less than 10% of babies with untreated ABO erythroblastosis. Kernicterus is nearly always preventable by exchange transfusion.

At Passavant Memorial Hospital, the cord blood of all babies born of Group O mothers is checked at birth paying attention to hemoglobin and RBC levels and particularly to bilirubin levels. A baby of group A or B must be carefully watched especially if the bilirubin level at birth is 5 mg. per cent or higher. If the bilirubin rises at a rate of 0.5 to 1.0 mg.% per hour, exchange transfusion will probably be necessary and should be carried out to prevent the bilirubin level from reaching 20 mg.%. A baby with liver or spleen enlargement will also be a candidate for transfusion. Usually one transfusion will suffice, but sometimes two and rarely three will be necessary to keep the bilirubin level below 20 mg. %. Using these criteria, we have transfused about ½ of 1% of all newborn babies at Passavant Memorial Hospital. In the past two years, we have had no fatalities due to ABO incompatibility.

– Edwin J. DeCosta, M.D.

PSYCHIATRY

Ainslie Meares, M.D.
Melbourne, Australia

Ainslie Meares is the author of twenty-five scientific papers and seven books on different aspects of psychiatry. He has worked with painting and modeling in the early diagnosis and treatment of schizophrenia. Several of his publications concern the techniques of interviewing. However, he is best known in the field of medical hypnosis. Last year he visited India, Kashmir, Nepal, and Burma studying the control of pain in yoga. He is president of The International Society for Clinical and Experimental Hypnosis.

RECOGNIZING THE SCHIZOPHRENIC BEFORE HE IS PSYCHOTIC

We can all recognize the full-blown schizophrenic. He is mad. He may hear voices, and he may tell us of things that are obviously delusional. He acts impulsively and unpredictably. He may show that strange smile, or laugh and giggle even when he talks of sad things, or he may remain apathetic and quite untouched by all that goes on around him. This is the illness when it is well advanced, and the patient may already carry the stigma of "insane," may have lost his job, and his home life may be seriously disrupted. But we can learn to recognize schizophrenia before any of these signs have developed; and with early psychotherapy and appropriate medication this terrible illness may be aborted.

Schizophrenia develops in persons of introvert personality. The apparent exceptions to this are cases of pseudo-extraversion, people who habitually cover up their shyness and sensitivity by a forced and rather unnatural bonhomie. The young introvert who is developing schizophrenia shows signs of it in his emotional responses, his thought and his behavior.

Emotional Responses

As schizophrenia first develops, the already sensitive introvert goes through a phase of heightened sensitivity. He soon comes to defend himself from this by emotional withdrawal. He protects himself by an indifference to things. This gradually

progresses to the blunting of affect and the apathy of the fully developed illness. The disordered emotional response may show itself as a strange wistfulness. This is the forerunner of emotional incongruity as seen when the schizophrenic smiles when he thinks sad thoughts. Sometimes there is a knowing smile that betrays those seeds of suspicion that later grow to paranoid thinking.

A change of the prevailing mood may mask the onset of schizophrenia. The other early signs of the illness may be overlooked, and the patient may be treated for his depression, with the result that the underlying schizophrenic condition remains untreated for some time. Sometimes there is mild euphoria and overactivity which may be associated with unexpressed ideas of mission or unity with God.

Anxiety is a very important sign of early schizophrenia. In fact, overt anxiety in a young introvert which does not show any clear psychogenesis, and which does not settle with mild medication and reassurance should always make us think of incipient schizophrenia. This anxiety is often accompanied by a vague feeling of disintegration, or by unaccustomed thoughts of homosexuality. These ideas are not usually ventilated in verbal communication, but if such patients be given painting materials or modeling clay these ideas find expression in the making of dismembered bodies and bisexual symbols.

Thought

The onset of schizophrenia is often preceded by changes in the individual's traditional way of looking at things. Characteristically, there is a devaluation of reality. He tends to become preoccupied with the pseudo-philosophical, the metaphysical and the mystical. He may become preoccupied with ideas of birth and death. This preoccupation is quite distinct from depressive thinking in which the patient feels that he should never have been born, or that he should expiate his guilt in death. It is also quite distinct from obsessive thinking about birth and death in which the patient is unable to make the normal transition to another topic of thought. It is more akin to Hamlet's pondering of death. The pondering of these ideas is the precursor of the delusions of giving birth to the God-child or of dying to save humanity. In this early stage of the illness the patient will often change in habitual patterns of religious and political thought. The case history of a schizophrenic very often discloses that the patient made an abrupt change of religion a few months before any evidence of psychosis was observed. Similarly, a change to communism in an introverted lad of a conservative household may precede the onset of more florid symptoms.

There are also changes in the actual way in which the patient thinks. He may show a tendency to symbolic thinking by talking in riddles or he may tend to answer a question by asking one himself. Schizophrenic thinking is often very literal, so that the patient is unable to comprehend any deeper meaning. This is easily tested by asking the patient the meaning of simple proverbs. If we ask him the meaning of the expression, "When the cat is away the mice will play," he is likely to reply by talking about cats and mice.

His thoughts may have a pre-delusional quality. For instance, the shy,

sensitive introvert may feel that people are looking at him, or talking about him. However, he can pull himself out of it as it were, by saying to himself, "I only think this because I am self-conscious." This is normal experience for introverts, and in itself it is not a sign of impending psychosis. However, if these ideas of reference develop a more compelling quality so that he cannot properly dismiss them, or if they come to influence his behavior so that he goes by a different street to avoid people, then the ideas of reference become a sign of pre-psychotic schizophrenia. A vague feeling that one's thoughts are being influenced by some outside agency such as electricity or hypnotism is a more significant sign. Ideas of mission not uncommonly precede a schizophrenic breakdown. The young man suddenly feels a need to do something to help mankind. A few months later such thoughts may become elaborated into typically grandiose ideas of divine mission or divine ancestry.

Behavior

Strangely enough, signs of either an increase or a decrease of introversion may warn us that the young introvert is developing schizophrenia. He may gradually withdraw from both his friends and his family. He may spend much time with his books in the pretense of study. As his fantasy life becomes more active, he may sit vacant, and out of touch with his immediate surroundings. His behavior may become tinged with a certain childishness. He may be inattentive and careless about his appearance. A girl who has previously dressed in good taste may come to dress inappropriately, or the different elements of her dress, her costume jewelry, and her make-up may fail to harmonize.

There may be signs of an apparent decrease of introversion which at first pleases the relatives. The introvert may start going to parties, whereas previously he was too shy. But his behavior is really incongruous. He acts over-hearty, as it were. We feel that it is not real. There may be a lack of social propriety. This is sometimes shown by the young introvert coming into the consulting room smoking, or the introvert of either sex may show an unexpected and inappropriate disregard of nakedness during physical examination.

The introvert is by nature idealistic. Prior to a schizophrenic breakdown this idealism may become disassociated from reality. The patient may feel a sudden need to become a missionary without any thought about practical matters such as training or equipment. Out of unrealistic idealism the introvert girl may seek marriage or sexual experience with some delinquent psychopath in the belief that she must help him. The patient's behavior reflects a general tendency to abandon practical reality. This may show itself in an interest in occult cults and esoteric practices.

An awkward stiffness of movement may be the forerunner of catatonia. Strange lower abdominal symptoms may precede schizophrenic ideas of homosexuality, and in a girl such symptoms may later be followed by the belief that she is about to give birth to the child of God.

The diagnosis of pre-psychotic schizophrenia is made by an evaluation of these signs, with special reference to any change in magnitude and to their meaning to the patient.

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Prescribing information adopted Jan. 1961.

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SURGERY

Felix Jansey, M.D.
Northwestern University

Felix Jansey is an Associate in the Department of Surgery at Northwestern University Medical School and Professor of Surgery at Cook County Graduate School of Medicine. A graduate of Rush Medical College, he is now Senior Attending Surgeon at Chicago Wesley Memorial Hospital and Attending Orthopedist at Cook County Hospital and Hines V. A. Hospital. Dr. Jansey is a Diplomate of the American Board of Surgery and a fellow of both the International and the American College of Surgeons.

INGROWN TOENAIL

There is an odd circumstance in the treatment of ingrown toenail that frequently changes it from a minor problem to a major one: it is a condition that is easy to relieve but hard to cure. Many techniques for treating the ingrown toenail give only temporary relief because they deal with the toenail rather than the flesh around it. "Ingrown toenail" implies that the disorder is the result of faulty toenail growth, but, on the contrary, the nail is ordinarily normal and healthy. If lexicographers had named it "nail-corner-cut-short; flesh-pushed-up," we would now be stuck with an awkward name, but perhaps our treatment would be more precisely directed.

Toenails Should Be Square

Ingrown toenail is most common in the large toe, because it has more soft tissue and bears more weight and more shoe pressure than a smaller toe. It occurs when the patient tries to make his toenails look like fingernails by enthusiastically trimming them to form artistic curves. Taking out the corner of the nail leaves a space, which is filled with soft tissue pushed up by the weight borne by the toe and crowded in by the surrounding shoe or the adjacent toe. When the growing toenail exerts painful pressure on the raised tissue, an ulcer forms. Inflammation and sometimes infection follow. The tissue becomes hypertrophied, hyperplastic, and fibrotic. To relieve the pain, the patient often cuts back the nail still more; this helps, but only until the growing nail again presses against the swollen tissue.

Most surgical procedures for ingrowing toenail are simply more radical versions of the patient's own nail-trimming efforts. The nail may be either partially or completely removed (Figure 1). The important dis-

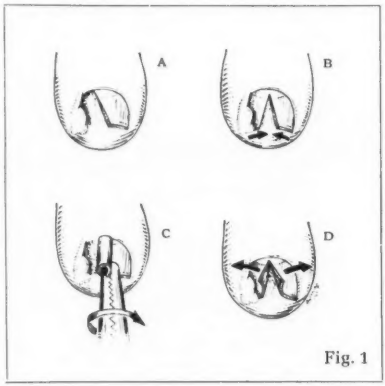

Fig. 1

advantage of these procedures is the high frequency of recurrence.

The wedge resection (Figure 2) attempts to correct the real problem by removing not the nail but the excess tissue. A lateral wedge of tissue is excised, and the wound is closed with sutures drawn tight to pull the swollen tissue away from the nail. The disadvantages: approximation may be

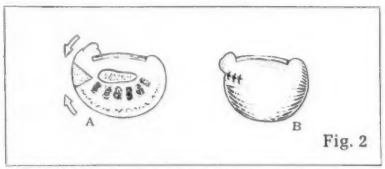

Fig. 2

difficult because fibrotic tissue is unyielding, and the sutures tend to pull through. More important, the offending fibrotic tissue remains.

A Better Operation

In my experience, these procedures are unsatisfactory because they are often followed by prolonged disability, recurrence is frequent, and the result unsightly.

In my operation, the hypertrophied nail fold rather than the nail is removed. As shown in Figure 3, the operation consists of two incisions, one straight and one curved, to form a D- or P-shaped wedge. Slip the scalpel blade between the nail and the overhanging tissue (A). Then make a deep (about ½"), straight incision following the nail margin and extending through the distal tip.

Begin the second incision at the proximal end of the first incision. As you draw the scalpel toward the distal tip (B), tilt the scalpel so that the incision curves away from the nail to encompass all the swollen tissue. Throughout the cut, the imbedded scalpel

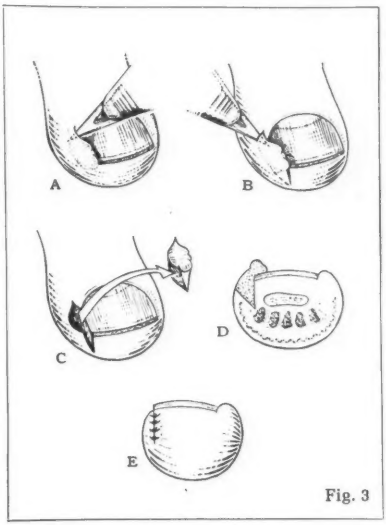

Fig. 3

point remains within the first incision so that, when the second incision joins the first at the distal tip, the wedge of tissue can be lifted free (C). All the

fibrosis, ulcer, and granuloma should be excised in one wedge. The scalpel strokes should be continuous to minimize trauma and leave smooth surfaces.

The lateral flap then may be approximated using a mattress suture. However, I find that this is seldom necessary. An encircling strip of adhesive, with a small glob of petrolatum or glycerine on it to prevent sticking, will usually suffice to hold the flap in place. Notice that removal of the wedge of tissue leaves the toe smaller (E); no fold of marginal tissue now projects over the nail. In this respect, the toe now resembles the finger, where little tissue protrudes over the nail—and, incidentally, where ingrown nails are rare.

In the 25 years since I first conceived this simple operation, it has served me well; only minimal complications have ever arisen. Healing is rapid and permanent because there is no tissue for the nail to grow into.

QUESTIONS AND ANSWERS

Q. *What anesthetic is used?*

A. It depends upon your patient. If he's apprehensive, you will probably want to use a general anesthetic; usually, however, local anesthetic is adequate. First, place a small rubber tube about the toe as a tourniquet to minimize oozing, which might obscure vision. Then inject 2 to 4 cc. procaine into each side of the first metatarsus deep enough to reach the digital nerves. Add a few cc. subcutaneously, but never inject the anesthetic directly into the thickened tissue, for this is painful and ineffective and may spread infection.

Q. *Are any of the non-surgical treatments effective?*

A. Soaks, ointments, topical anesthetics give only temporary relief. The placing of a tuft of cotton under the nail might succeed if the patient has the persistence to continue until the nail has grown beyond the lateral fold; unfortunately such persistence is rare. The cotton does not relieve the pain completely, so the patient usually resorts to cutting back the nail corner again. Temporary relief results, but final cure is delayed.

Q. *Can't recurrence be prevented by permanent removal of the nail?*

A. Of course. It requires excision of the nail matrix along with the adjacent layers of the stratum germinativum and the stratum corneum in the zone of transformation. Because the zone of transformation lacks a distinctive appearance or a separable cleavage plane, excision may be inadequate, and a deformed nail may regenerate. Obviously, the patient may object to permanent ablation of the nail. Who wants a toe with no nail or only part of one?

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PROCTOLOGY

J. Peerman Nesselrod, M.D.
Santa Barbara Cottage Hospital

From 1955 to 1960, J. Peerman Nesselrod was Assistant Professor of Surgery at Northwestern University and Chief of Proctology at Evanston Hospital. At present he is on the active staff, Santa Barbara Cottage Hospital, Santa Barbara, California. A Captain in the United States Naval Reserve, member of the American Proctologic Society and American College of Surgeons, he is the author of CLINICAL PROCTOLOGY (Saunders).

SOME REMINDERS FOR MANAGEMENT OF THE PROCTOSCOPIC EXAMINATION

Proctoscopy remains a sadly neglected procedure in physical diagnosis. No thorough physical examination is complete without proctoscopy, and certainly no study of the terminal gut should be concluded without endoscopy.

Selected for discussion herein are several factors that can determine either success or failure of the procedure.

Preparation of the bowel, essential to good visibility, is easily accomplished by means of 2 or 3 warm tap water enemas taken by an out-patient 1 or 2 hours prior to examination. For the in-patient, warm tap water enemas are given the preceding evening, and a Fleet enema (sodium phosphate and sodium biphosphate) is administered in the morning one hour before the examination. The Fleet enema is easily self-administered by most patients, and is useful in the office for patients who, for some reason, are not adequately prepared.

Nothing is to be gained by examining a patient whose bowel is not prepared. Examination of the stool is best done in the clinical laboratory. Anyone who is suffering from an acutely painful anal condition should not be expected

to take cleansing enemas or to tolerate examination without adequate analgesia or anesthesia.

The *inverted position* is best in most instances, and is accomplished by using a tilt-type, proctoscopic table. No matter what table is used, however, the examiner must take time to position his patient carefully.

The knee-shoulder position, properly effected, is excellent for proctoscopy, but requires that the patient divide his attention between holding himself in position and listening to the examiner. It is thus not suitable for the patient who is weak or acutely ill.

The left Sims' position is acceptable for the bedridden patient, especially if the examining table can be tilted slightly.

Conduct of the Examination. By his conduct of the proctoscopic study the examiner can establish rapport with his patient, or he can completely demoralize him. I have seen an inexperienced examiner place a patient on the table, *suddenly* tip him forward, *suddenly* force a finger into the rectum, remove the finger *suddenly* and *suddenly* insert a proctoscope—all without one word of warning or explanation! The inevitable fiasco affects adversely both patient and examining physician.

In this article the need for brevity obviates adequate discussion, but let us start the examination by asking the patient to loosen or to remove any tight clothing. Simple, explanatory statements should precede every step in the procedure in order to avoid startling the patient and to gain his confidence. Extreme gentleness in all manipulations is mandatory.

Inspection and palpation are the basic points of physical diagnosis involved in proctoscopy. I was startled recently to observe a senior resident insert a proctoscope in a patient's rectum without preliminary external inspection and digital anorectal palpation! The examiner must never insert the endoscope without preliminary, careful, digital exploration of the anal canal and rectum to determine the presence or absence of stool, stenosis or obstruction.

The less experienced examiner often fails to make full and proper use of digital rectal palpation. It would help him to keep in mind a simple classification of rectal lesions: intraluminal, intrinsic (mucosal and/or submucosal), intramural and extrinsic or extrarectal. The differentiation between intramural and extramural lesions is not easy. Too, the physician should realize how easily he can overlook, on palpation, a soft mass of polypoid tissue, especially should it be pediculate.

In his consideration of extra-rectal (extramural) lesions the examiner will be aided by remembering normal structures palpable anteriorly, laterally and posteriorly. Students and house officers are encouraged to correlate their findings on palpation with those found on endoscopy, at laparotomy, and at necropsy.

Proctoscopy (proctosigmoidoscopy) is actually *internal* inspection. With the patient's abdomen "hanging free" and his anal canal rendered patent by the endoscope, one atmosphere of pressure is established in the terminal gut, which then tends to fall cephalad out of the true pelvis. This is an important

advantage of the inverted position, and is especially helpful to the less experienced examiner. The obturator is removed as soon as the tip of the instrument has entered the distal rectum. Further progress of the instrument should be accomplished under direct vision—*never blindly!* It is usually easy to reach the rectosigmoid area, some 12-15 cm. above the anus. Here, however, the examiner may have difficulty in finding the lumen of the gut. The problem is that of the "blind pouch," which is a formidable barrier to the inexperienced examiner and accounts for many instances of inadequate proctoscopy. The inexperienced examiner usually fails to recognize the difficulty, and therefore fails to solve it. Air inflation here is useless.

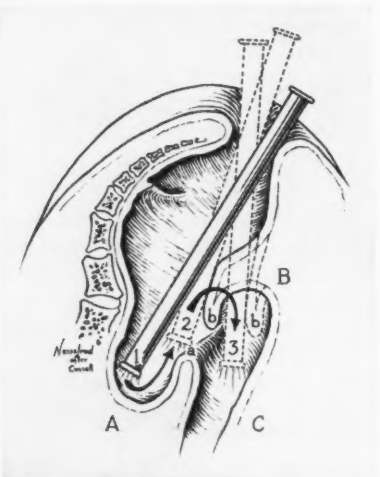

Figure 1. Diagrammatic representation of further endoscopic maneuvers. Blind pouch seen at A. The numeral 1 indicates the proctoscope lying in the blind pouch at A. The numerals 2 and 3, together with the arrows, designate succeeding positions of the proctoscope during its withdrawal from the blind pouch and its passage into the more proximal limb, BC, of the sigmoid colon. (Modified from Nesselrod's CLINICAL PROCTOLOGY.)

In the figure, the tip of the instrument in position 1 lies in the blind pouch at A. It is easy to overlook the lumen hidden by fold "b" overlapping fold "a." If the examiner, holding the endoscope in his left hand and using his left wrist as a "fulcrum," will carefully and slowly withdraw the instrument he will note fold "b" and will observe that it can be moved either laterally or anteriorly disclosing fold "a" when the tip of the instrument lies in position 2. In addition this gentle maneuver discloses the lumen of the more proximal limb BC, into which the instrument can be easily passed, i.e., position 3 at C.

Points A and C are approximately equidistant from the anus. Assuming that the distal limb AB of the loop ABC is 3 cm. in length and that the proximal limb BC is 3 or more cm. in length, one can conclude that the endoscopist who reaches point C has observed at least 6 cm. more bowel than has the less experienced examiner who was content to stop at point A.

Let me add a word of warning to the examining physician about the ever-present danger of perforation. Under no circumstance should he force the instrument, or attempt to pass it without exact knowledge concerning the location of the lumen and the integrity of the tissues of the gut wall.

Having focused his attention thus far on the safe introduction of the endoscope, the examiner can concentrate on thorough inspection during the withdrawal of the instrument. He must make every effort to view carefully all surfaces. Two maneuvers are especially helpful here. 1) He should be careful to "iron out" all folds by

means of a clockwise sweep of the instrument during its withdrawal in order that lesions such as small polyps will not be overlooked. 2) The physician should become aware of the difficulty of visualizing the posterior rectal wall, especially the distal half, unless he depresses the proximal end of the endoscope toward the patient's perineum, just as he did during the introduction of the instrument. It should be remembered that the long axis of both anal canal and proximal rectum is at a right angle to the long axis of the distal rectum.

If the patient has a very narrow margin of nervous reserve, because of a painful anal lesion, he should be given the benefit of regional anesthesia.

The less experienced examiner should avoid removing tissue for microscopic study unless he is prepared to control bleeding that can sometimes be a serious problem.

In conclusion, let me suggest the following "do's" and "don'ts."

Do's:

1) Insist upon proper preparation.

2) Use inverted position wherever possible.

3) Ask patient to loosen or to remove tight clothing.

4) Conduct examination with extreme gentleness and provide explanatory remarks (vocal anesthesia).

5) Concentrate on the safe introduction of the instrument. Then focus on examination during withdrawal of the instrument.

Don'ts:

1) Don't forget careful inspection.

2) Don't forget careful digital palpation.

3) Don't force the instrument.

4) Don't pass the instrument blindly (except through the anal canal).

5) Don't forget that it is possible to perforate the bowel.

QUESTIONS AND ANSWERS

Q. *When is it necessary to use air inflation in the examination?*

A. When one encounters a "sticky" bowel, in which the gut walls do not "fall away" easily, it is safer to use gentle air inflation in identifying the lumen.

Q. *What type of regional anesthesia do you recommend for proctoscopic examination?*

A. 1) Caudal, 2) sacral or low spinal.

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OBSTETRICS

William J. Dignam, M.D.
U.C.L.A.

William J. Dignam is Associate Professor of Obstetrics and Gynecology at U.C.L.A. School of Medicine. He graduated from Harvard Medical School, interned at Boston City Hospital, and completed his residency at University of Kansas School of Medicine. A Diplomate of the American Board of Obstetrics and Gynecology, Dr. Dignam is a member of the staff of St. Johns Hospital, Santa Monica, City of Hope Medical Center, Duarte, and the University of California Medical Center, Los Angeles.

POSTPARTUM HEMORRHAGE

Postpartum hemorrhage is still a major cause of maternal death, deaths that are preventable if the emergency is met with well-planned action. Sometimes the hemorrhage cannot be foreseen; frequently, though, there are predisposing conditions that should lead us to foresee trouble and to prepare for it.

Hypofibrinogenemia is one such condition, although not a common one. It is much too complicated to discuss in this short paper; nevertheless, two things about it are worth mentioning. The coagulability of the blood always should be tested during labor. The blood should clot within ten minutes in a dry test tube, and the clot should be stable. Also, on every obstetric ward, there should be at least 8 gm. of fibrinogen on hand, and every obstetrician should learn how to mix it before an emergency arises.

More common than clotting defects as a forewarning of possible hemorrhage is uterine atony. When the uterus is overdistended – as it is in mothers with large babies, hydramnios, or multiple pregnancies – we should be particularly alert for signs of hemorrhage. Poor uterine contractions during the later phases of labor (especially likely in fatigued women of high parity) should also alert us to possible hemorrhage. A uterus which is contracting well often stops completely when a spinal anesthetic is adminis-

tered. When it does, bleeding is likely after delivery of the placenta.

Prophylactic Therapy

When I see any of these predisposing conditions, I advise prophylactic therapy as follows. Place an 18-gauge needle securely in a vein, draw blood for typing and crossmatching, and begin a 5% glucose-in-water infusion. As soon as the placenta is delivered, add one milliliter of pitocin per 1000 ml. of glucose infusion, and allow it to run rapidly in order to keep the uterus forcefully contracted to prevent excessive bleeding.

Proper management of the third stage of labor can frequently prevent hemorrhage. Do not manipulate the uterus before separation of the placenta, for that might partially dislodge the placenta and actually start bleeding. Instead, as soon as possible after delivery of the baby, place your hand upon the fundus of the uterus in order to feel it change to a globular shape when the placenta separates. This also helps you to be certain that the uterus is not filling with blood. After placental separation, you may apply gentle fundal pressure to express the placenta from the cervix and vagina. If this fails, examination frequently reveals the placenta lodged in the vagina or cervix. As soon as it is removed, the uterus will contract and bleeding will probably cease. Of course, if the mother begins to bleed profusely (more than 400 ml.) before the placenta is delivered, the placenta should be removed manually from the uterus.

Bleeding Without Warning

But what do you do if bleeding begins without warning? No prophylactic measures have been taken, so quick action is imperative to avoid tragedy.

There is some solace in the fact that the great majority of these bleeding episodes are due to uterine atony, and proper massage will control this bleeding in most cases. First, insert the hand into the vagina and press the fingers against the cervix; it will feel soft and floppy. Lift the uterus out of the pelvis and into the abdomen. At the same time, place the other hand on the fundus and vigorously massage the uterus between your hands. Usually, profuse bleeding will be controlled within one or two minutes. If not, an anesthetist should be called if one is not already present. Meantime, with an 18-gauge needle, take blood for crossmatching and begin an intravenous glucose infusion. Inject one milliliter of undiluted pitocin directly into the i.v. tube, and add one ml. per 1000 ml. of glucose in the infusion bottle. If the situation is too urgent to delay whole-blood transfusion until the crossmatch is complete, immediately give O-negative blood, with Witebsky substance added for greater safety.

As soon as an anesthetist arrives and the infusion is running, begin to administer an anesthetic that will permit good oxygenation, such as cyclopropane. Carefully explore the vagina and uterus for lacerations or retained fragments of the placenta. Careful exploration is important because it is so easy to overlook a sizable laceration behind a redundant fold of mucosa. Good lighting and good exposure are essential. If found, the laceration should be repaired with chromic 0 suture; hemostasis must be complete. Large lacerations in the upper part of the uterus may require abdominal surgical exploration.

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If neither lacerations nor retained placenta is found, I believe that uterine packing does have value, if properly done in properly selected patients. First, massage the uterus to make it as firm as possible. Then, holding the uterine fundus in the palm of one hand, pack the uterine cavity securely with wide gauze. Pack cervix and vagina in the same way. After packing, a continuous infusion of one ml. of pitocin per 1000 ml. of 5% glucose in water is given for 8 hours. The pack is removed after 24 hours, meantime the mother is kept under careful observation.

Hysterectomy is seldom, if ever, needed to control postpartum bleeding due to uterine atony. When a hysterectomy is performed, frequently a laceration is found which has been overlooked.

Postpartum bleeding is a serious emergency; yet it can almost always be controlled by prompt action, well planned in advance.

QUESTIONS AND ANSWERS

Q. *Are plasma extenders useful in managing postpartum hemorrhage?*

A. Yes, but only as a temporary substitute for whole blood. Whole blood is so superior that, in extreme emergency, you are justified in giving blood of the patient's type or O-negative blood, without crossmatching, until matched blood arrives.

Q. *Do you advise using vasopressor agents to control hemorrhage?*

A. No, hemorrhage should be combatted by replacement with whole blood. Vasopressors may raise blood pressure and reassure the physician, but they do so by vasoconstriction, which may impair blood supply to vital organs, such as the kidneys.

Q. *Isn't fibrinogen expensive? Is the expense justified when hypofibrinogenemia is so rare?*

A. Eight grams of fibrinogen costs about $132 and can be stored almost indefinitely. If it saves just one life, I think it's worth the cost.

Q. *Do you feel that ergot derivatives are helpful for controlling bleeding?*

A. If bleeding is profuse, i.v. preparations are essential. I think that i.v. pitocin is superior to i.v. ergot derivatives because hypertension is less of a problem. However, i.m. ergonovine may be used if the patient isn't responding to pitocin.

Q. *Is there danger of postpartum bleeding from vulvar varicosities?*

A. Yes, this can be a problem. In order to avoid rupturing varicosities, try to do the episiotomy in an area free from them. If varicosities are lacerated during labor, try to control bleeding by pressure rather than by sutures, for sutures frequently perforate still other varicosities.

Q. *Is postpartum bleeding more likely when bleeding has occurred in late pregnancy?*

A. Yes, both abruptio placenta and placenta previa may cause postpartum bleeding. Abruptio placenta may predispose the patient to postpartum hemorrhage in two ways: first, bleeding due to abruptio placenta may be caused by hypofibrinogenemia, and second, uterine atony may result from damage to the uterine muscle caused by abruptio placenta. The former is treated by administration of fibrinogen, the latter by massage.

Placenta previa may result in a fragile, soft, poorly contracting lower uterine segment that bleeds profusely after delivery—even delivery by cesarean section. This area of the uterus is so fragile that you must be very careful not to tear it during delivery. If bleeding does occur, it's best treated by uterine packing.

Q. *Is there danger of hypopituitarism following profuse bleeding?*

A. Yes, it may be a major complication. Inability of the mother to lactate may be the only immediate indication of pituitary damage, so patients who have hemorrhaged during labor should be investigated for possible hypopituitarism within a few months after delivery.

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Herbert O. Sieker, M.D.
Duke University

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WHAT THE OCULAR FUNDUS SHOWS ABOUT SYSTEMIC DISEASE

The ocular fundus gives us the unusual opportunity of looking directly at a portion of the circulation and central nervous system and of seeing there the earliest signs of many systemic diseases. The view we get also helps us to determine the severity of an illness and to judge objectively its response to therapy. In this short review, I will highlight the ocular characteristics that I have found useful.

Hypertension and Nephritis

The earliest ophthalmoscopic signs are essentially the same in all types of hypertensive vascular disease and nephritis. Nephritis should be suspected, however, when the degree of renal insufficiency is proportionately greater than the retinopathy.

In these diseases, the fundus is plethoric and the retinal arteries are tortuous and pulsating. Usually the earliest, consistently reliable sign is a diminution of the caliber of the retinal artery and arterioles with a decrease in the ratio of artery to vein from ⅔ to less than ⅓. The caliber of arterioles varies because of areas of focal spasm and regions of irreversible sclerosis. The arteriolar light reflex is abnormal, with a relative decrease in its width and a change in color, either to a vivid copper tone or a silvery luster commonly described as "silver wire." This, in turn, progresses to a dull,

white, thread-like linear strand that represents the obliterated vessel in advanced stages of hypertension. Arteriovenous compression, or nicking, occurs as a result of increased resistance in the arteriolar walls. While perivascular sheathing is not peculiar to hypertension, it is observed frequently. Often thrombosis and fragmentation of arterioles will be noted, and neovascularization frequently occurs in regions deprived of normal blood supply.

While the etiology of hemorrhages and exudates is not known, it appears to be related to arteriolar disease that interferes with nutrition and oxygenation of adjacent retina. With damage to the capillary walls, transudation of high-protein fluid into the retinal tissue and diapedisis of red cells occur. Irregular, flame-shaped hemorrhages are seen in the superficial layer of the retina; they are darker, well-defined, and tend to be in dot or blot arrangements in the deep layers. In some types of hypertension the retina develops a sheen and becomes somewhat pale, suggesting generalized edema. Papilledema occurs with cerebral edema and increased intracranial pressure in malignant hypertension.

Diabetes Mellitus

In general, the degree of diabetic retinopathy correlates with the severity of small blood vessel disease, particularly in the kidney. Many of the vascular and retinal changes described for hypertensive disease and nephritis are also seen in diabetes, but certain abnormalities are seen more frequently or specifically. Early in diabetes, venules tend to be dilated and sausage-shaped, and, as the disease progresses, you can actually see segmentation of the blood column, due to sludging. Neovascularization is more common and extensive in diabetic than in hypertensive retinopathy. The early characteristic hemorrhage is small, well-defined, and punctate, since it occurs in the deep layers of the retina. Often bleeding in the superficial areas of the retina extends into the vitreous, with resultant scarring and neovascularization. Papilledema occurs usually only in association with hypertension or marked renal failure.

In hyperlipemic conditions, including severe diabetes, the retinal vessels are flattened and dilated and assume a pinkish, salmon, or white color. The optic disc is grayish and the fundus, while it preserves its reddish hue, appears darker.

Although retinal degeneration has been reported with arteriosclerosis of the retinal vessels, in my experience it usually occurs in association with such degenerative small blood vessel diseases as diabetes and hypertension. Arteriosclerosis in large vessels, such as the coronary arteries, is not accompanied by evidence of vascular changes on funduscopic examination unless there is also associated small blood vessel disease.

Blood Dyscrasias

Blood loss alone, when it is marked, may cause blurring of the optic disc margins, paleness of the optic nerve, flame-shaped hemorrhages, and white ill-defined exudates. These changes are rapidly reversed with restoration of blood volume. In pernicious anemia the arteries may be narrowed, and hemorrhages may be numerous and flame-shaped. Often a white spot appears in the center of the hemorrhage or a white fringe appears at the edge. Other types of anemia may show sim-

ilar changes, particularly sickle cell anemia, where you will see extremely tortuous venules.

Dilated dark veins can be seen in polycythemia, either primary or secondary. The disc is redder and small hemorrhages may be seen in the retina.

In leukemia about one-third of the cases will show the retina and vessels developing a pale yellowish or orange hue. In myelogenous leukemia, hemorrhages may be massive and often have a white center.

In thrombocytopenia purpura and other diseases in which coagulability of the blood is decreased, retinopathy can occur, but it is much less frequent than in anemias and leukemias. Occasionally, mild optic neuritis may be observed.

Illnesses With Disturbed Blood O_2, CO_2

In cyanotic congenital heart disease with associated polycythemia, the retinopathy is quite similar to that described for polycythemia. Although not well-recognized, the hypoventilation syndromes – including chronic lung disease, obesity, and neuromuscular disorders – may show dilated and darkened retinal arterioles and venules with hyperemia of the optic disc, resulting from hypoxemia or hypercapnia. Occasionally, with marked hypoventilation, hemorrhages, exudates, and papilledema occur, making differential diagnosis from brain tumor difficult.

Infectious and Granulomatous Diseases

Syphilis, although less common since the advent of penicillin therapy, may cause acute inflammation of the retina, with hyperemia of the optic disc, edema, and exudation around the nerve head. Later, atrophic patches and pigmentation appear in the retina, collecting around retinal vessels as a perivascular retinal pigmentation. Tuberculosis may involve the retina and presents the picture of grayish-white exudates covering the vessels or adjacent to them. Vessel congestion and hemorrhages may appear. As the disease recedes, white, atrophic scars with pigmentary changes remain. Sarcoidosis and fungus diseases, such as blastomycosis, may also show retinal exudates similar to those of tuberculosis.

Septicemias, particularly subacute bacterial endocarditis, may produce retinopathy, presumably because small emboli containing bacteria lodge in the vessels. Numerous white spots near the optic disc and hemorrhages with white centers are often observed.

Neurologic Diseases

Any conditions producing increased intracranial pressure, such as tumor, abscess, or hemorrhage, may be manifest by fundus abnormalities that include loss of venous pulsation, venous engorgement, papilledema, and superficial retinal hemorrhages. Illnesses of obscure etiology, such as multiple sclerosis, may show their first signs as abnormalities in the eye, with symptoms and findings of papillitis. Similarly, many toxic nervous system diseases, such as methyl alcohol poisoning, show papillitis.

As this brief résumé of fundus changes in non-ocular diseases shows, careful examination of the eyegrounds with the ophthalmoscope is helpful in the diagnosis and evaluation of many systemic diseases.

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INTERNAL MEDICINE

Perk Lee Davis, M.D.
Davis Clinic—Paoli Medical Center

Perk Lee Davis is Director of the Davis Clinic – Paoli Medical Center in Pennsylvania. During World War II, he was Chief of Cancer Wards at Walter Reed Hospital. Currently a consultant in oncology to the Surgeon General of the Armed Services and to the United States Naval Hospital in Philadelphia, he is a member of the Pennsylvania State Cancer Commission and of the Philadelphia County Medical Society Cancer Committee. He is a member of the American Board of Internal Medicine and of the American College of Physicians.

SUBTLE SIGNS OF CANCER AND LEUKEMIA

We are all on the look-out for overt signs of cancer, certainly the much publicized "seven danger signals." These signs are easy to recognize; but unfortunately they usually point to a fairly advanced stage of cancer. To save more lives, we need signs that will make us suspect cancer still earlier. Fortunately there are at least a few such signs; they will be found among our patients' vague, seemingly neurotic complaints.

For example, cancer and leukemia patients often have numerous and vague complaints, the kind we impatiently refer to as an "organ recital." Or they may have only one really strange complaint, maybe a rectal discomfort they cannot describe, or a headache that is somehow different, or a "funny, itchy feeling." Such complaints are easily dismissed with a shrug, or a referral to a psychiatrist. Too often, in fact, that is just what happens. Many a cancer patient has come to me on referral from a psychiatrist who realized, after fruitless sessions, that the patient's symptoms could not be explained by his mental status. These patients, and many others, could have been helped much earlier (and possibly have been cured) if their physician had taken their vague, early complaints seriously.

Here are some signs that are often associated with very early malignancy yet are usually misread because they seem to point to another disease—usually neurosis. Every one of these signs, however vague, mild, or neu-

rotic-sounding, is on record as a possible early clue to cancer, and should alert you to suspect cancer until you have done a complete physical examination–including a thorough history, blood studies, and appropriate tissue studies. Remember that a complete physical examination always should include scrupulous examination of all lymph-node-bearing areas.

Skin Problems

Unexplained complaints of itching – vague, generalized, or local – may be associated with leukemia, Hodgkin's disease or other malignancy. You should also suspect all unexplained skin eruptions; hidden cancer may cause lesions that mimic scabies, tuberculosis, meningococcemia, fungus infections, and skin sensitivity to detergents. Be especially alert to recognize acanthosis nigricans–a thickened black eruption on the body, usually found in the axilla; it may be the first sign of a malignancy. Physical examination in patients with unexplained skin lesions should include (after thorough examination of the lesions to establish etiology) a general physical examination for possible underlying malignancy.

Headache

Headache may be a sign of leukemia, primary brain tumor, or metastatic cancer. For example, severe, generalized headache is characteristic in children with leukemia. Of course, the headache may not be distinguishable from common headaches such as migraine, or histamine headache; however, in some cases it may distinguish itself merely by being vaguely different. The patient may say: "Doctor, this isn't the same kind of headache I've had before." Diagnostic tests in patients with headache should always include, in addition to neurological examination, a fundoscopic examination, X-ray, and peripheral blood and bone marrow studies, if indicated.

Bone and Joints, Fever

Bone and joint pain, with or without chills and fever, may be an early indication of multiple myeloma, leukemia, or sarcoma of the bone. The pain may be mild and sporadically recurrent; it can be confused with rheumatic fever, "growing pains," subacute bacterial endocarditis, bacterial or viral infection, or Sickle cell anemia. Persistent symptoms that mimic influenza are a common early finding in patients with acute leukemia. In patients with such complaints, whenever a thorough history and diagnostic tests do not support a diagnosis of infection, examine the patient again, this time with cancer in mind.

Weakness, Fatigue

Weakness and fatigue that have no physical basis are subtle symptoms that may be your only clue to an otherwise asymptomatic malignancy. Whenever the usual causes of weakness such as hyperthyroidism, myasthenia gravis, diabetes, anemia, iron deficiency, and blood loss have been ruled out, suspect cancer. Only when the latter has also been ruled out can you safely decide that weakness and fatigue are psychosomatic.

Cough or Hoarseness

Cough or hoarseness that lasts more than three weeks is not always the result of the overuse of tobacco, or to a cold that is just "hanging on." They should prompt – at least – chest X-ray, sputum specimen study, and examination with the laryngeal mirror.

Urinary Symptoms

Any change in urinary function or habit, such as difficulty in urination or blood in the urine (gross or microscopic), should be investigated thoroughly. In addition to examination of the prostate, and urine chemistry tests, the investigation should include microscopic inspection of the urine sediment after centrifugation and appropriate staining; this sediment may contain bacteria or extruded cancer cells from the kidney, bladder, or prostate. Other symptoms referrable to cancer of the urinary system include enlargement of the kidney, and tenderness to percussion and palpation. In some cases, the only clue to early urinary cancer may be a pain in the back at the costovertebral angle.

Gastrointestinal Symptoms

Any *change* in digestive function should alert you to look for possible cancer. Such a change may be one of the familiar cancer symptoms such as persistent indigestion. Or, it may be a more subtle, unusual symptom. A fairly common one in patients with early leukemia is a peculiar rectal discomfort which the patient cannot describe and which is not accompanied by a local lesion. A vague feeling of rectal fullness is a common early complaint in patients with rectosigmoid cancer. Another common finding in leukemic states is enlargement of the spleen or liver, sometimes without lymph node enlargement. All such complaints should be investigated thoroughly with complete physical examination, X-ray, and blood studies. I would like to emphasize that, in patients with rectal complaints, mere digital examination is not enough; 86% of all rectosigmoid cancers occur beyond the reach of the examining finger and sigmoidoscopy is absolutely necessary.

Bruising, Bleeding, or Petechiae

Unexplained bleeding or any persistent sore may point to early cancer and requires thorough testing which should include the appropriate endoscopic examinations. Even a common complaint like "frequent blood on the toothbrush" can be significant, if it is unusual for the patient in question. Incidentally, an important point to remember when examining the mouth—with or without a lesion—is to palpate the floor of the mouth and the nasopharynx; this simple maneuver is often overlooked, yet it frequently reveals enlarged lymph nodes and areas of thickening in the mucosa which would prompt a search for cancer of the nasopharynx.

An unusual tendency to bruise should prompt thorough blood and bone marrow studies, including blood count, bleeding and clotting time, platelet count, total blood proteins, prothrombin (percentage, time and P.T.A., and P.T.C. factors), fibrinogen, and vitamin C level. These studies will help to differentiate between a malignant disorder and other causes such as vitamin C deficiency, capillary fragility, and thrombocytopenic purpura.

Obviously, many of the signs and symptoms I've listed here are not always indicative of cancer. Nor should we become overconcerned about the possibility of cancer at every vague symptom; certainly, we don't want to intensify a true neurosis by needless testing. But whenever a patient who is reasonably stable complains of a new, vague or bizarre symptom, at least consider the possibility that it may be the only clue to an otherwise silent malignancy.

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NOTE: Total daily dosage should not exceed 5 mg. for children ages 2 and under, 10 mg. for children ages 3-6, or 15 mg. for children ages 7-12. The physician should caution parents not to administer more than prescribed dosage to children.

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Prescribing information adopted January, 1961

GASTROENTEROLOGY

Cyrus E. Rubin, M.D.
University of Washington

Cyrus E. Rubin is Associate Professor in the Department of Medicine at the University of Washington in Seattle, and is an Attending Physician at the King County and Seattle VA Hospitals. A member of the American Gastroenterological Association, he has done research on the mucosa of the small intestine in malabsorption. He and his collaborators have developed several peroral biopsy techniques which they have used extensively for diagnosis and clinical research, not only in the small bowel but also in the stomach and rectum.

PERORAL SMALL BOWEL BIOPSY: A USEFUL, ACCURATE PROCEDURE

In the past, the diagnosis of celiac disease, or idiopathic sprue, was often uncertain; and knowledge of the intestinal pathology involved—based as it was on autolysed post-mortem material or occasional surgical biopsies—was incomplete and confused.

In recent years Dicke and his colleagues have proved the gluten-free diet is an effective treatment and others have developed methods by which diagnosis can be made accurately and quickly. Consequently, recognition of patients with celiac disease and idiopathic sprue has become of great practical importance.

This paper describes peroral biopsy of the small bowel—the method that has become the prime technique for diagnosing celiac sprue.

The Disease

Celiac disease in children and idiopathic sprue in adults are known by many names: idiopathic steatorrhea, nontropical sprue, adult celiac disease, gluten-induced enteropathy, primary intestinal malabsorption, etc. Evidence now available suggests these are really different phases of the same disease. Advances in our knowledge may shortly justify a name which refers to its etiology, but until we have a more complete understanding of its pathogenesis, I will refer to it as celiac sprue, a combination of the more frequently used traditional names.

Experimental work in patients with celiac sprue has shown the lesion to regress partially or even completely when gluten, the protein fraction of wheat and rye, is removed from the diet. On the gluten-free diet the patient also recovers clinically. Reintroduction of the gluten causes prompt recurrence of the illness and injures the bowel wall. This inability of the patient to handle gluten is probably a permanent hereditary defect.

Peroral Suction Biopsy

Wood and Tomenius introduced the idea of peroral suction biopsy of the gastric mucosa more than 10 years ago. At the present time there are a number of instruments that, although they vary somewhat in design, use this basic idea to obtain biopsies from the esophagus, stomach, duodenum, jejunum, ileum, and colon. These instruments consist of a small diameter tube with a capsule at one end. The tube itself is rigid enough to advance the capsule rapidly, yet flexible enough to negotiate the sharp turns of the intestine. The biopsy is obtained by sucking a small knuckle of intestinal mucosa through a hole in the side wall of the capsule.

This mucosal knuckle is then excised either by pulling a cylindrical knife with a wire or by various hydraulic mechanisms. Precise control of suction and a sharp, durable cutting system insure clean excision of every biopsy with minimal trauma to the specimen. With a properly designed instrument used by an expert operator, the danger of hemorrhage is minimal and the likelihood of perforation just about nonexistent. With the newer instruments for proximal intestinal biopsy, two specimens can be obtained in as little as 15 minutes. The procedure is safe and dependable and can be used in infants as well as adults.

The appearance of the normal bowel mucosa may vary considerably from one individual to another, but in general a biopsy obtained from a normal intestine will show the surface to be covered with numerous slender villi that contain a rich network of capillaries. The appearance of the small bowel surface in patients with celiac sprue presents a marked contrast. The villi are blunted or may be absent altogether, thus reducing the epithelial surface. The lamina propria is infiltrated to a varying extent with chronic inflammatory cells, and the epithelial cells themselves are often abnormal. This difference is usually sufficiently obvious to be seen with an ordinary magnifying glass, although, of course, it is difficult to differentiate milder lesions this way. Despite the obvious nature of this lesion its existence had been denied for years until Paulley clearly pointed out that this lesion did indeed exist.

To test the validity of our histologic interpretations, we had three different observers in our laboratories evaluate coded biopsies, without clinical foreknowledge, from over 200 patients. We used biopsies from all of our 60 patients with celiac sprue and included at random those from 150 patients who were either normal or had other types of malabsorption. The observers in this blind evaluation diagnosed celiac sprue correctly in all 60 of the patients who had it; moreover, they did not diagnose it in any of the 150 who did not.

While it is becoming more and more widely used, peroral suction biopsy is

not employed as a diagnostic technique at every medical center, for the technique of handling the specimens is relatively new and requires special training. Because the specimens are very small and the histologic alterations often subtle, they must be handled very carefully by both the physician who mounts them and the adept histology technician who sections them. Otherwise, reliable diagnoses are impossible; artifacts due to tangential sectioning are easily misinterpreted as abnormalities. To maintain exact orientation the fresh tissue must be mounted precisely, and atraumatically, on a plastic mesh immediately before fixation, and the whole biopsy must then be sectioned serially. The tissue cannot, for instance, be carelessly tossed into fixative and sectioned as would be done in the usual routine pathology procedure.

Peroral Biopsy in Other Small Bowel Disease

There are other illnesses that cause a diffuse change in the small bowel and that may be diagnosed by peroral suction biopsy. One is tropical sprue, which causes histologic changes like the ones seen in celiac sprue although it is a distinctly different disease both clinically and pathogenetically. Fortunately, it offers little diagnostic confusion in the continental United States because it is not seen here.

Peroral biopsy is also of diagnostic value in Whipple's disease, which may be recognized by the typical macrophages containing sickle-shaped particles; these cells fill the lamina propria of the villi and blunt them and are positive to the PAS (periodic acid-Schiff) stain. Diffuse small bowel lymphoma may be diagnosed rarely. Regional enteritis is very hard to biopsy by this method, because it is a spotty lesion that is predominantly distal, and impaired peristalsis associated with the illness usually makes it impossible to reach the involved area. There is little doubt that other entities will be defined in the near future as the peroral suction biopsy method becomes more popular.

QUESTIONS AND ANSWERS

Q. *Is the celiac sprue lesion seen in other malabsorption syndromes?*

A. There have been an increasing number of claims that it is. But I think most, if not all, of these claims can be attributed to artifacts caused by improper handling of the biopsy. I believe that the lesion is specific for celiac sprue; its absence rules out the diagnosis in a patient who is taking a normal diet containing gluten.

Q. *What medical centers that you know of have facilities available for peroral biopsy?*

A. More all the time. A specific answer is impossible.

Q. *Since treatment of celiac sprue is so simple, why not use the treatment itself as a diagnostic tool, rather than put the patient to the trouble and expense involved in referring him to a university center?*

A. Treatment is not simple. It takes considerable effort to follow a strict gluten-free diet; furthermore, the diet should be continued throughout life if further trouble is to be avoided. An unequivocal, objective diagnosis provides the best motivation for both the physician and his patient to follow this long-term regimen. There are also some nonspecific responses to a gluten-free diet in other diseases.

Q. *Are there other intestinal allergies that can be detected by this method?*

A. There is no good evidence that celiac sprue is allergic in etiology. It is far more likely that it is an inherited metabolic defect which interferes with normal gluten metabolism. "Intestinal allergy" as a cause of chronic symptoms in adults is in my opinion nonexistent.

Q. *Wouldn't it be possible to have the biopsy done and send the specimen to a lab for evaluation, rather than send the patient?*

A. Taking a small bowel biopsy and processing it properly are both essential for correct diagnosis. This requires special skill and merits consultation with a gastroenterologist trained in the technique. Moreover, there is more to the diagnosis and management of this illness than taking the biopsy. These patients may be very ill and because of the rarity of the illness consultation with a specialist is always useful.

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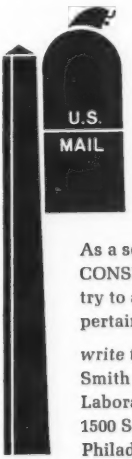

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DERMATOLOGY

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Eugene M. Farber is a Professor of Dermatology and the Director of the Department of Dermatology at Stanford Medical Center. He is a graduate of the University of Buffalo School of Medicine. Active in both research and teaching at Stanford, he also serves as National Consultant to Surgeon General, Department of Air Force; on the Board of Directors, Society for Investigative Dermatology; and as a Consultant, Council on Pharmacy and Chemistry, A.M.A. His many publications, contributions to several books, and a book on leg ulcers, now in progress, indicate his wide interests.

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PSORIASIS—A DIFFICULT DISEASE

Psoriasis is a capricious skin disease that affects four million people in the United States alone. Its chronic and disfiguring nature is extremely distressing to the patient, and at times its recalcitrance to therapy makes it a frustrating problem to the physician. Its cause or causes remain unknown.

Unless properly selected, therapeutic countermeasures can often do more harm than good.

Recognition of Psoriasis

Usually, diagnosis presents few problems. Lesions are distinctively silvery-gray scaling papules or plaques with the predilection for the scalp, knees, elbows, sacrum, genitalia, and intertriginous areas. When chronic, the lesion margins show a sharp transition from involved to normal skin. Psoriatic lesions on the scalp may resemble seborrheic dermatitis, but generally are more sharply marginated and not as greasy.

Psoriasis may range from a few small chronic lesions to a severe, diffuse, exfoliative eruption. It may be of no concern to the afflicted or it may be very incapacitating. Self-medication with certain all-purpose remedies often will cause a relatively static condition to become worse.

Pretreatment Considerations

The person with psoriasis who goes from one doctor to another looking for a "cure" has probably never had a complete explanation of its nature, the difficulties of treatment, and the probability of control or eradication. The physician should inform the afflicted that the disease may wax and wane in severity and will perhaps never disappear completely. He should reassure the patient that psoriasis is not infectious, contagious, or likely to cause serious systemic symptoms.

Although the cause of psoriasis is not known, certain factors which determine or alter its course have been discovered. Strong evidence implicates heredity; about 30% of the patients have a family history of psoriasis. In identical twins, both will generally have the disease. A strong genetic background frequently suggests an unfavorable course. Psychic stress may initiate or exacerbate psoriasis. Chemical or mechanical trauma associated with a new job may bring on psoriasis or make worse an otherwise static eruption. Diet, recent infections, and some anti-arthritic drugs may aggravate its course. Appraisal of these factors will aid in outlining the prognosis and therapy.

Treating Psoriasis

Management is necessarily non-specific; however, some measures have consistently been more helpful than others. Coal tar as a 2-5% solution in hydrophilic ointment USP is more acceptable than the older, messy, grease-type ointments. Applications should be made repeatedly during the day and supplemented with exposure of affected areas to sunshine whenever practical. Mineral-oil-impregnated cotton may be used to remove old ointment before each reapplication. As an alternate treatment, full strength coal tar solution USP may be applied to the lesion with a cotton tipped applicator.

Application of ammoniated mercury 2-5% ointment, several times a day, is also frequently effective. If the lesions are quite thickened, 1.5-3% salicylic acid can be added to the ointment, but one must be alert for possible irritation. For scalp lesions an ointment containing 2-10% ammoniated mercury and 1-4% salicylic acid in a water miscible base may be applied several times daily. A daily tar shampoo

is advisable when scalp psoriasis is severe.

Anthralin in a 0.1 to 1% ointment concentration is often of value. It is advisable to start with a low concentration and work up, thereby lessening the likelihood of irritation. Because it stains as well as irritates, it should not be used in the scalp or near the eyes.

In advanced cases of psoriasis the Goeckerman regimen is the best and safest treatment program developed to date. It usually provides partial remissions for 5 months or more in about 75% of those treated. It consists of repetitious daily application of 2-5% crude coal tar and exposure to ultraviolet irradiation in increasing sub-erythema doses. This method, which is necessarily messy and disagreeable, is best carried out with the patient hospitalized for at least several weeks. A modified Goeckerman regimen can be applied at home, but it requires an unusually conscientious patient to carry it out.

Systemic Agents

Arsenic, aminopterin, and corticosteroids are the best known systemic drugs, but all produce toxic reactions serious enough to contraindicate their use in the usual case of psoriasis. Corticosteroids should be reserved for "life-saving situations," since they can cause an exacerbation of psoriasis when withdrawn.

Iatrogenic Psoriasis

Chloroquine and certain other antimalarial drugs, when employed in treating arthritis, not only can aggravate psoriasis but may indeed precipitate its initial development. Adrenocorticosteroids are at times employed to reduce the extent of psoriasis; but when discontinued, they almost inevitably cause an exacerbation that is not only severe, but is atypical in appearance and resistant to therapy.

General Principles

No matter what measures one uses to treat psoriasis, several general principles should be kept in mind:

1) When psoriasis is rapidly spreading, it is far better to employ conservative measures, such as lubricating cream and perhaps cautious exposures to ultraviolet light or sunlight, than to risk aggravating the disease by vigorous treatments.

2) Topical treatments, no matter how useful at first, may gradually lose their effectiveness; it is thus well to maintain some of them in reserve rather than to use them all in rapid succession.

3) Reassurance and psychological support are worthwhile and frequently necessary. When psychic stress and tension appear prominent, rest and relaxation are essential.

QUESTIONS AND ANSWERS

Q. *Are psoriasis and arthritis related in any way?*

A. Arthritides and psoriasis frequently co-exist. The arthritis may be of the rheumatoid type but is more commonly a specific "psoriatic-arthritis." Psoriatic arthritis differs from rheumatoid arthritis

on 5 major counts: absence of rheumatoid nodules, asymmetry of joint involvement, negative latex fixation test, frequent involvement of terminal interphalangeal joints, and at times marked bone destruction about arthritic joints.

Q. *What drug measures can be used to treat persons with psoriatic arthritis?*

A. Salicylates combined with physiotherapy constitute the safest approach. Corticosteroids and antimalarial drugs are not advisable as a rule.

Q. *What measures do you suggest to control psoriasis that follows the use of steroids?*

A. Hospitalization for several weeks so that rest, diet, and bland topical care can be instituted. As the inflammation becomes less severe the Goeckerman regimen can then be instituted.

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ALLERGY

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Samuel M. Feinberg is Professor of Medicine and Director of the Allergy Unit at Northwestern University Medical School. He received his medical training at Rush Medical College. He has been President of the American Academy of Allergy, 1942-44, and the International Association of Allergology, 1955-58. He is the author of six books on allergy and has published 250 papers. For many years, he also has directed the training of selected specialists in allergy.

INSECTS: A CAUSE OF ALARMING AND PUZZLING ALLERGIES

I think insects are to blame for more allergic symptoms than is generally supposed. The alarming and even fatal anaphylactic reactions resulting from bee stings in susceptible patients have, of course, made us all more aware that insects can be more than just pests, but I suspect that a good many of these cases are mistaken for heat prostration or heart failure. Also, we are not likely to incriminate insects in hay fever or asthma, yet inhaled insect scales, hairs, and other body fragments have been traced as the cause of many puzzling and stubborn cases of seasonal allergy. With summer already upon us, I would like to review briefly the diagnostic, prophylactic, and therapeutic measures in insect stings and inhaled insect allergies.

Insect Stings

The moderate local swellings produced by bites from mosquitoes, mites, bees, and other insects are due to the irritating chemical substances in the insect's venom, which is not allergenic in most persons. But in those who are allergic to it, an immediate and severe reaction can occur, principally from bee stings, and may consist of large local swellings, generalized urticaria and angioedema, asthma, and even anaphylactic shock and death. Tests have shown these

manifestations are truly allergic; sensitive persons react to a protein present both in the venom and in the body of the insect. On occasion, a delayed "serum sickness" reaction may result 8 to 12 days after a bee sting and consist of generalized swellings, joint pains, and fever.

Stings from honeybees, bumblebees, yellow jackets, wasps, hornets – the hymenoptera – cause most of the allergic reactions. The patient, however, seldom knows which insect stung him. Since the antigens in insect venom are not all alike, I have found it best to assume that the susceptible patient needs protection from all the major species of stinging insects.

The diagnosis of "bee" allergy may be confirmed by scratch tests. If they are positive, no further tests are necessary. If negative, intradermal tests should be made, beginning with about 1:1 million dilution.

I have seen good evidence, and others have too, that desensitization gives considerable prophylactic protection. I regard it practical to use an extract prepared from a mixture of the common stinging insects. However, it is usually necessary to treat sensitive persons continuously for a long period of time to maintain immunity.

Emergency treatment consists of giving adrenalin (0.5 cc. of 1:1,000) intramuscularly followed by a smaller amount (0.1 to 0.2 cc.) at the site of the sting. The adrenalin may be repeated once or twice at 5 to 10 minute intervals. Immediately following, a tourniquet should be applied proximally. In addition, antihistamines may be given intramuscularly or intravenously. Aminophylline for asthma may also be advisable, if breathing irregularities develop. Since corticosteroids or ACTH require hours for action, they are not useful as emergency measures.

On country trips, it would be well to advise sensitive persons to go with someone who knows how to administer emergency treatment. They should be advised to carry Isuprel-ephedrine tablets and to use them sublingually in case they are stung. It is a good idea for them to carry a hypodermic loaded with adrenalin or a disposable sterilized syringe with a rubber stoppered vial of adrenalin.

Inhaled Allergens

As I have said, it isn't only the venom of insects that can cause trouble for the allergic patient, but inhaled allergens too. The connection between asthma and hay fever symptoms and exposure to such insects (I am using the term loosely here to include some arthropods) as May flies, caddis flies, aphids, house flies, beetles, mites, and others has been recognized for some time. But the connection between respiratory allergy and the inhalation of insect particles has generally been overlooked, even though the connection is common. Evidence for it includes: the frequency of reactions in scratch tests to a variety of insects; the pattern of seasonal cases not explained by molds or pollens alone; the improvement with proper specific desensitization measures.

Since allergy is usually of multiple etiology, the exact clinical role of a single antigen cannot always be distinguished conclusively. Only the minority of patients who react to insect particles react to them alone, but this is similarly true for patients who re-

act to pollens, molds, and other antigens. In an analysis of 600 patients with seasonal allergic reactions, my colleagues and I were able to determine that in only 22 per cent of those who reacted to insects could insects be pinpointed as the cause. With molds, it was 35 per cent; with grass pollens, 22 per cent. As I say, this is due primarily to the overlapping and frequently similar associated reactions to these antigens in the same patient.

The indications are that insect dusts are important causes of asthma and hay fever from spring to fall. The farther south you go, the more frequently insects appear to be a prime cause of respiratory allergy. In subtropical regions, where pollens are of minor importance, insect allergens are probably the predominant cause. As mentioned before, it is seldom necessary to make a diagnosis by intradermal tests. If done, it should be remembered that insect extracts contain irritants capable of giving false reactions, and must, therefore, be used in a non-irritating concentration.

Since hundreds of thousands of insect species exist, the types used for diagnostic and desensitizing purposes must be selected carefully. Their selection should be governed by availability of sources, likelihood of exposure to related groups, and their ability to produce positive skin tests frequently. Although a large variety has been used in testing, I have used mainly silk pupa (representing the moth family), house fly, May fly, ant pupa, and daphne for desensitization purposes.

Desensitization therapy is usually begun with a 1:100,000 dilution of an extract (weight by volume) with a maximum goal usually of 1:100. It runs very much the same as schedules and problems of desensitization with other antigens. And with it, we have come to expect the same general results, that is, approximately, 85 per cent satisfactory protection.

Next month in CONSULTANT:

Meat Impaction in the Esophagus, by Eddy D. Palmer, Col., M.C.—an article telling how to handle an increasingly common medical emergency in elderly people.

Office Management of Anal Lesions—a practical article by L. Kraeer Ferguson, M.D., giving pointers on examination, minor surgery, and follow-up care.

Without question the standard drug for weight reduction

is widely accepted, superbly documented 'Dexedrine'. Because it not only controls appetite but also encourages mental and physical activity, 'Dexedrine' renews the patient's interest in life, reduces her chronic and frequently morbid yearning for food.

DEXEDRINE® *Smith Kline & French Laboratories, Philadelphia*

brand of dextro amphetamine

Formula—Each 'Dexedrine' Tablet contains dextro amphetamine sulfate, 5 mg. **Indications**—For the control of appetite in weight reduction, depressive states, alcoholism, narcolepsy. **Dosage**—For weight control, up to 30 mg. daily, in doses of 5 to 10 mg., 30 to 60 minutes before meals. For depressive states and alcoholism: up to 30 mg. daily in doses of 5 to 10 mg. at intervals of 4 to 6 hours. For narcolepsy: up to 50 mg. daily. **Side effects**—insomnia, excitability and increased motor activity—are infrequent and ordinarily mild. **Cautions**—Use 'Dexedrine' with caution in patients hypersensitive to sympathomimetics, in coronary or cardiovascular disease, in severe hypertension. **Contraindications**—Agitated pre-psychotic states and hyperexcitability. **Available**—5 mg. tablets, in bottles of 100.

Prescribing information adopted January, 1961.

SPECIAL FEATURE

Maxwell L. Gelfand, M.D.
New York University

Maxwell L. Gelfand is Associate Professor of Clinical Medicine at New York University Medical Center. He is associated with New York University, Knickerbocker, and Bellevue Hospitals, and is consultant to the Meadowbrook Hospital. A Fellow of the American College of Physicians and of the New York Academy of Medicine, he is a member of the New York and American Heart Associations. In the May issue of CONSULTANT, Dr. Gelfand wrote on diagnostic clues to be learned from looking at the patient; this month he writes on the diagnostic value of the stethoscope.

AUSCULTATION: A NEGLECTED ART

*"Three dollars puts the stethoscope in the hands of the medical student. Its initial cost is trivial, its maintenance and depreciation charges are not worth mentioning, it does not require an extra room at fifty dollars or more to house it, and no extra charges are made to the patient if it proves necessary to use it. It is portable, convenient, and almost indestructible. Although some doctors neglect it or use it carelessly, it richly rewards the man who uses it painstakingly. No patient is too poor or too disabled to have the benefits of its use. Regardless of age, sex, or religion, the stethoscope is available for everyone within reach of a doctor. It is applicable in the hospital, in the home, or on the street corner. It pours its secrets unreservedly into the ears of him who will only listen and brings great fame to him who learns to interpret its small voice."** A quarter century has passed since Dr. Waring felt it necessary to remind us of the virtues of this simple instrument. Nevertheless there are many doctors today who think only of complicated electronic devices and radioactive materials when confronted with a diagnostic problem. More than ever we are tempted to forget that much can be learned with a simple technique—auscultation.

Cardiac Disorders

Sharp accentuation of the first apical sound may be the earliest clue to mitral stenosis, and should alert the

*James J. Waring, Presidential Address at the 32nd Annual Meeting of the National Tuberculosis Association, 1936.

examiner to the presystolic or early mid-diastolic murmur so characteristic of this disease. Frequently the mere presence of an accentuated first heart sound in the absence of the tell-tale murmur is enough to indicate this condition when auricular fibrillation also exists. Accentuation of the first heart sound may also be due to other factors — hyperthyroidism, anemia, fever, tachycardia, or a short P-R interval. Decreased intensity of the first heart sound at the apex may be the earliest sign of a first degree heart block.

The second heart sound is accentuated and of a tambour quality in luetic, arteriosclerotic, and hypertensive heart disease. The relation between the aortic second sound and the pulmonic second sound is even more important. When P2 is markedly accentuated and greater than A2 in adults, pulmonary hypertension — i.e., mitral stenosis, left ventricular failure, or cor pulmonale — should be considered. Wide splitting of the second sound, unaffected by respiration, is indicative of an atrial septal defect with a high pulmonary flow. Bundle branch block may also produce abnormal splitting of the second heart sound. In complete right bundle branch block, wide splitting of the second heart sound during expiration, with further increase of the splitting during inspiration, occurs; this is best heard over the pulmonic area. In left bundle branch block the splitting of the second sound is paradoxic, resulting during expiration in a widely split second sound which disappears or diminishes during inspiration.

Pulsus alternans, a regular sinus rhythm with an alternating strong and weak beat, and a diastolic gallop rhythm, may be the first manifestations of heart failure.

Cardiac murmurs are significant and extremely informative, but the examiner must remember that they may also be heard in cases of high fever, anemia, tachycardia, nervousness, hyperthyroidism, or during exercise. In aortic stenosis the systolic murmur is transmitted to the vessels of the neck, and often it radiates to the apex; at times it may best be heard there.

Diastolic murmurs are even more important than systolic murmurs, but they too must be carefully differentiated. Diastolic murmurs at the apex may indicate 1) mitral stenosis, 2) aortic regurgitation (Austin-Flint), 3) acute rheumatic carditis (Carey-Coombs murmur), 4) ventricular and atrial septal defects, 5) patent ductus arteriosus, or 6) sickle cell anemia. A continuous murmur heard over the pulmonary valve is characteristic of patent ductus arteriosus. Murmurs heard over other areas of the body—trunk, extremities, neck, or head—are due to arteriovenous fistulas (aneurysms) of any type.

Local Vascular Pathology

Systolic murmurs over the various arteries in the body, without compression of the vessels (which in itself can cause murmurs) may reveal local abnormalities. A murmur, sometimes with a thrill, may be felt over an aneurysm anywhere in the body, i.e., the carotid, subclavian, renal, femoral, popliteal and the abdominal aorta. Thus no physical examination is complete without placing the stethoscope over these areas. A bruit over the carotid artery or temporal artery suggests either carotid artery insufficiency or thrombosis.

Pulmonary Disorders

Consolidation, cavitation, pneumothorax, hydrothorax, atelectasis, and asthma are serious disorders that can easily be detected by auscultation long before an X-ray film dries. An expiratory sound phase prolonged throughout expiration indicates tubular or bronchial breathing. This is heard normally over the trachea, the primary bronchi, a limited area at the right apex, and over the right interscapular area; heard elsewhere, it connotes a pathologic process such as lobar pneumonia or atelectasis. Increased whispered voice and egophony have the same general significance as bronchial breathing; they appear earlier and are more easily heard, but are slightly less reliable. Amphoric breathing indicates a pulmonary cavity, and diminished breath sounds are found over collapsed pulmonary tissue, i.e., atelectasis, pneumothorax, hydrothorax, pulmonary edema, or passive congestion. Shaking the chest while the stethoscope is applied sometimes causes the succussion splash which indicates hydropneumothorax. The tinkling sound of two coins struck together is transmitted through the chest in cases of pneumothorax. A unilateral wheeze heard either anteriorly or posteriorly is a possible sign of an obstructive lesion, a foreign body, or a neoplasm. Sudden disappearance of the wheeze previously audible in a severe asthmatic, together with diminution in the intensity of the breath sounds, may be a manifestation of complete blocking of the bronchioles; it carries a poor prognosis.

Rales that do not disappear on coughing may have considerable significance. Dry rales are usually heard in inflammation of the mucous membranes of the bronchi when tenacious mucus partially occludes them; moist rales indicate fluid in the bronchi or alveoli and are most commonly heard in cases of lobar pneumonia, bronchitis, tuberculosis, and cardiac failure. Fine moist rales at the apices of the lungs are important diagnostic signs in early tuberculosis, and crepitant rales are found in lobar pneumonia during engorgement and resolution, in pulmonary edema, and in early stages of tuberculosis.

Abdominal Disorders

Peristalsis increases during early intestinal obstruction, but is absent in the full-blown condition; at this time, the stethoscope applied to the abdomen will reveal a significant silence. A lesion of the esophagus may be suspected if the epigastric splash occurs more than seven seconds after the patient has swallowed a mouthful of water. A rub in the upper left quadrant may indicate a splenic infarct, and one in the upper right quadrant, an hepatic infarct. It has been suggested that a rub can be heard over the anterior surface of the liver in cases of secondary metastases, whereas in primary hepatic carcinoma no rub will be heard. A continuous venous hum in the area between the xiphoid and umbilicus in the presence of a visible collateral circulation is indicative of the Cruveilhier-Baumgarten syndrome.

These are a few of the clues offered to the educated ear. All they require is a quiet room, a patient relaxed and completely undressed, a stethoscope, and the art of auscultation. Auscultation increases the value of percussion, palpation, and inspection; it should be neither discarded nor neglected. Let the slogan of the stethoscopist be: "Listen, think, and listen again".

Of 39 women treated for long-term infertility with 'Cytomel'

18 became pregnant

13 with amenorrhea began to menstruate regularly

From a report by Foster, H.M.: Am. J. Obst. & Gynec. 77:130 (Jan.) 1959.

CYTOMEL®

brand of liothyronine

ADMINISTRATION AND DOSAGE: Dosage should be adjusted according to the severity of the condition and the response of the patient.

Most patients should be started on 25 mcg. of 'Cytomel' daily. To increase dosage to recommended maintenance levels for these patients, increments of 12.5 or 25 mcg. may be made in the daily dosage at intervals of one or two weeks. Dosages in the range of 100 mcg. daily, and higher, are well tolerated by many patients.

When starting dosage is 5 mcg. daily (as in myxedema, male infertility, simple goiter and in patients being switched from thyroid, L-thyroxine, or thyroglobulin), increments of 5 or 10 mcg. may be made in the daily dosage at intervals of one or two weeks. When dosage reaches 25 mcg. daily, increase as described above.

'Cytomel' is usually administered in divided doses.

Note: In geriatric patients or in children always start with 5 mcg. daily and adjust dosage in increments no greater than 5 mcg.

Indication	Recommended Starting Dose	Recommended Maintenance Dose
Hypometabolism Mild Hypothyroidism	25 mcg. daily	25-75 mcg. daily (Smaller doses may be fully effective in some patients.)
Myxedema	5 mcg. daily	50-100 mcg. daily
Female Reproductive Disorders	25 mcg. daily	25-50 mcg. daily
Male Infertility (Based on sperm count or sperm motility responses after two to four weeks of treatment at a given dosage level, the daily dosage may be increased by 5 or 10 mcg. If after further treatment the desired response has still not been obtained, the daily dosage may again be increased. Although total daily dosage usually need not exceed 25 mcg., as much as 50 mcg. daily may be used if necessary.)	5 mcg. daily	10-25 mcg. daily
Simple (non-toxic) Goiter	5 mcg. daily	25-75 mcg. daily

SPECIAL CONSIDERATIONS AND CAUTIONS: Tachycardia, excitability, headache, or excessive sweating are signs of overdosage. Medication should be interrupted until the unpleasant symptoms disappear, and then resumed in smaller doses. Since the return to pretreatment status is rapid, 'Cytomel' can usually be resumed at the desired dosage after one to two days.

When a subnormal BMR exists as part of the clinical syndrome of hypometabolism or hypothyroidism, administration in excessive dosage will cause elevation of BMR to levels above normal.

'Cytomel', unlike various forms and fractions of thyroid, will not cause elevation of the blood protein iodine level.

Endogenous thyroid gland function, reflected particularly by I^{131} uptake, may be depressed by 'Cytomel' administration. Depression of this function is most apt to occur with higher dosages (greater than 75 mcg. daily). Experience to date indicates that this effect is not clinically harmful. There have been no unfavorable sequelae in reported instances where 'Cytomel' therapy has been discontinued after depression of I^{131} uptake occurred. In such cases this function has promptly returned to normal after discontinuance of 'Cytomel'.

Since 'Cytomel' is physiologically related to thyroxine, it is not recommended for use in the presence of angina pectoris, in other cardiovascular disorders, or ischemic states. However, if it is used in the presence of such conditions, the starting dosage should never be more than 5 mcg. daily. If dosage is increased, it should be in increments of no more than 5 mcg. daily at approximately two-week intervals.

Hypopituitarism, morphologic hypogonadism and nephrosis should be ruled out before 'Cytomel' is administered.

CONTRAINDICATION: Addison's disease.

FORMULA: Each 'Cytomel' tablet contains 5 mcg. or 25 mcg. of liothyronine (L-triiodothyronine or LT3), as the sodium salt; 25 mcg. of 'Cytomel' is calorigenically equivalent to approximately 1 gr. of thyroid.

AVAILABLE IN TWO DOSAGE STRENGTHS: 25 mcg. (scored) tablets in bottles of 100 and 1000; 5 mcg. tablets in bottles of 100.

Prescribing information adopted Jan. 1961

SK&F Smith Kline & French Laboratories

FOR QUICK CONTROL OF AGITATED BEHAVIOR

With 'Thorazine'—particularly the injectable form—you can quickly control severe agitation in patients such as alcoholics, seniles and hyperkinetic children. Belligerence and excitement usually give way promptly to more rational behavior, and the patient becomes receptive to guidance and counselling.

'Thorazine' is so effective in calming agitated patients because it provides:

- *a potent tranquilizing action* which controls emotional agitation.
- *an initial sedative effect* for control of physical hyperactivity during the first few days of therapy.

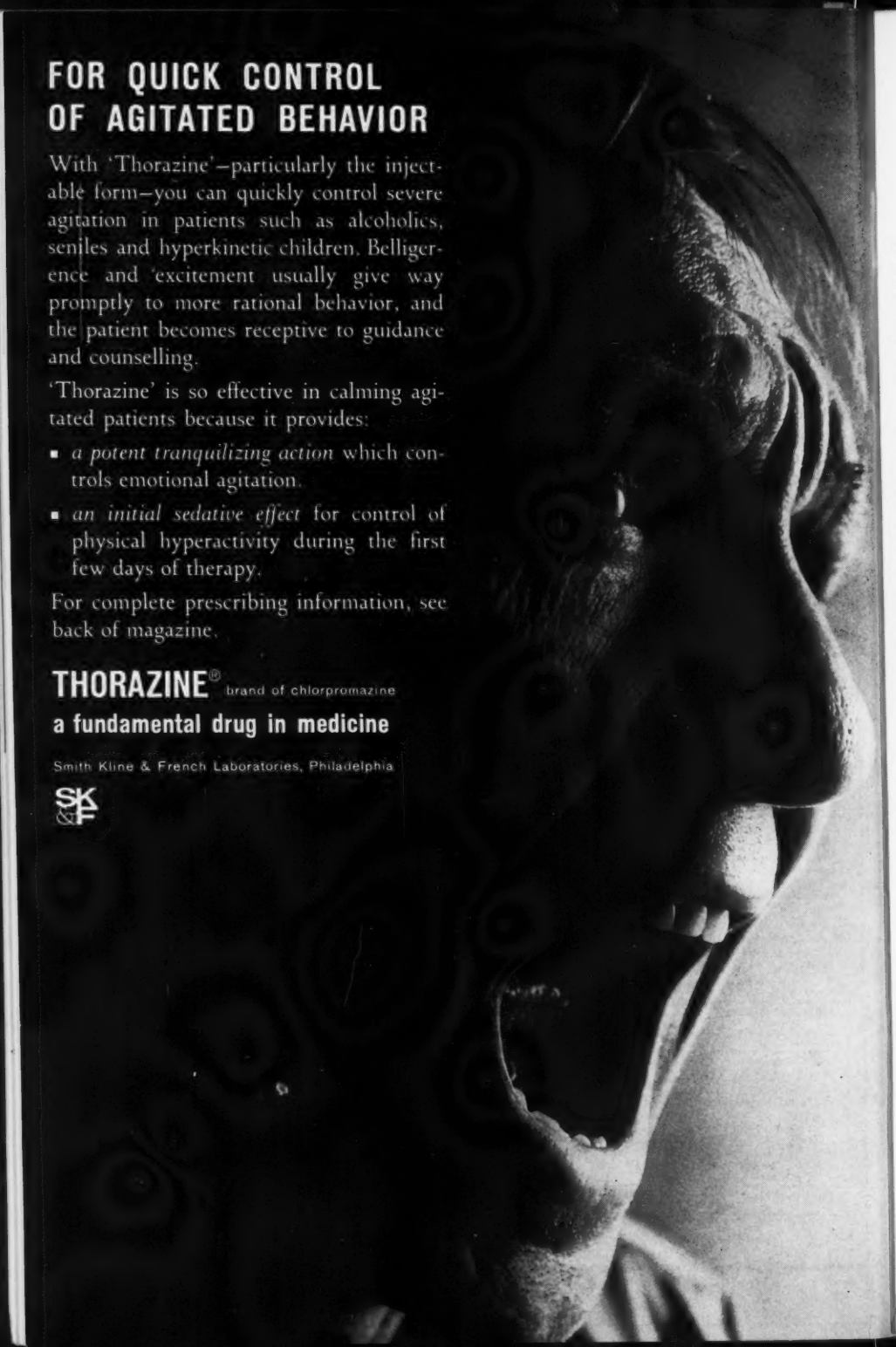
For complete prescribing information, see back of magazine.

THORAZINE® brand of chlorpromazine

a fundamental drug in medicine

Smith Kline & French Laboratories, Philadelphia

SK&F



THORAZINE®
brand of chlorpromazine

PRESCRIBING INFORMATION

Tranquilizer • Antiemetic • Potentiator

The wide diversity of clinical applications in which 'Thorazine' is valuable, as either a specific or an adjuvant, is due to its three fundamental clinical properties: (1) its capacity to alleviate anxiety, tension and agitation without dulling mental acuity, (2) its ability to potentiate sedatives, narcotics and anesthetics, and (3) its profound antiemetic effect.

The tranquilizing effect of 'Thorazine' accounts for its usefulness in somatic conditions where emotional stress is a factor, as well as in mental and emotional disturbances *per se*.

INDICATIONS

The value of 'Thorazine' is established in the following conditions:

Moderate to severe mental and emotional disturbances of everyday practice, particularly those disturbances marked by agitation, tension, apprehension, excitement, or anxiety.

Somatic conditions complicated by emotional stress, such as arthritis, tuberculosis, severe tension headaches, gastrointestinal disorders, dermatologic conditions, status asthmaticus and severe asthma.

Hospitalized psychiatric patients, to control agitation, dispel delusions and hallucinations, and at the same time to restore or increase the patient's capacity to respond to psychotherapy.

Nausea, vomiting and hiccups, with dramatic results in severe and refractory cases.

Acute or chronic alcoholism, to control agitation, delirium tremens, and nausea and vomiting.

Cancer, as an adjuvant, to control apprehension, suffering due to pain, and nausea and vomiting.

Intractable pain, to reduce suffering and to potentiate narcotics or sedatives.

Obstetrics, as an adjuvant, to control apprehension, pain, and nausea and vomiting. 'Thorazine' allows a reduction in the amounts of the drugs ordinarily used in obstetrical management, thus lessening the risk of respiratory depression in mother and infant.

Surgery, as an adjuvant, to control anxiety and apprehension, pain, and nausea and vomiting; and to reduce by potentiation the amounts of narcotics, sedatives and anesthetics needed.

ADULT DOSAGE AND ADMINISTRATION

Dosage should always be adjusted to the response of the individual and the severity of the condition. It is important to increase dosage until symptoms are controlled or side effects become troublesome.

Mental and Emotional Disturbances of Everyday Practice – Depending on severity, *starting oral dosage* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. After a day or two, dosage may be increased by increments of 20 mg. to 50 mg. daily, at semiweekly intervals (increase should be more gradual in emaciated or senile patients) until achieving maximum clinical response. Continue dosage at this level for at least two weeks; then it can usually be reduced to a maintenance level. A daily dosage of 200 mg. is "average," but in some cases, such as discharged mental patients, daily dosages as high as 800 mg. may be necessary. *Starting intramuscular dose* is 25 mg. (1 cc.). If necessary, and if no hypotension occurs, repeat the initial dose in one hour. Subsequent dosages should be oral, starting at 25 mg. to 50 mg. t.i.d.

Somatic Conditions Complicated by Emotional Stress–*Starting oral dosage* is 10 mg. to 25 mg. t.i.d. or q.i.d. Increase gradually by 10 mg. to 25 mg. increments at semiweekly or weekly intervals. *Starting intramuscular dosage* is 25 mg. (1 cc.), repeated after one hour if necessary and if no hypotension occurs.

Hospitalized Psychiatric Patients – ***Acutely agitated, manic, or disturbed patients:*** *Starting intramuscular dose* is 25 mg. (1 cc.). If no marked hypotension occurs, an additional 25 mg. to 50 mg. injection may be given after one hour. Subsequent intramuscular dosages may be increased gradually over a period of several days – even up to 400 mg. q4-6h in exceptionally severe cases – until the patient is controlled. (In elderly or emaciated patients the dosage should be increased more slowly than in other patients.) Usually the patient becomes quiet and cooperative within 24 to 48 hours after the initial dose, at which time oral doses may gradually be substituted for intramuscular doses (mg. for mg. or higher). Even if control is not complete, oral doses may gradually replace intramuscular doses. During this period, oral dosage should be increased rapidly until the patient is calm. Usually an *oral dose* of 500 mg. a day is sufficient but, if necessary, the dosage may be gradually increased still further to 2,000 mg. a day or higher. ***Less acutely agitated patients:*** *Starting oral dose* is 25 mg. t.i.d. Subsequently, increase the amount gradually until an effective dosage is reached – usually 400 mg. daily is sufficient. ***Duration of therapy:*** It is important to determine the optimal dosage regimen and to continue treatment long enough for maximum clinical response. Maximum improvement is sometimes not apparent until after weeks or even months of therapy.

Nausea and Vomiting – *Starting oral dosage* is 10 mg. to 25 mg. q4-6h, p.r.n., and may be increased if necessary. *Starting intramuscular dose* is 25 mg. (1 cc.). If no hypotension occurs subsequent doses of 25 mg. to 50 mg. q3-4h, p.r.n., may be given until vomiting is checked. Then replace intramuscular administration with oral. *Starting rectal dosage* is one 100 mg. suppository q6-8h, p.r.n. In some patients, one-half this dose may be sufficient.

Hiccups – *Starting oral dosage* is 25 mg. to 50 mg. t.i.d. or q.i.d. If after 2-3 days symptoms persist, *an intramuscular dosage* of 25 mg. to 50 mg. (1-2 cc.) may be used. *Use intravenous administration* only when symptoms still persist. By slow infusion, 25 mg. to 50 mg. (1-2 cc.) should be administered in 500 cc. to 1,000 cc. of physiologic saline solution, with the patient kept flat in bed. Follow blood pressure closely.

Alcoholism – ***Severely agitated patients:*** *Starting intramuscular dose* is 25 mg. to 50 mg. (1-2 cc.). Repeat initial dose if necessary and if no hypotension occurs. Start subsequent oral dosages at 25 mg. to 50 mg. t.i.d. ***Agitated but manageable patients:*** *Starting oral dose* is 50 mg., followed by 25 mg. to 50 mg. t.i.d. ***Ambulatory patients with withdrawal symptoms or sober chronic alcoholics:*** *Starting oral dose* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. Patients in a stuporous condition should be allowed to sleep off some of the effects of the alcohol before 'Thorazine' is administered.

Cancer and Pain – ***Severe pain:*** *starting intramuscular dosage* is 25 mg. (1 cc.) b.i.d. or t.i.d. ***Milder pain:*** starting oral *dosage* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. Because 'Thorazine' potentiates their action, reduce the dosage of narcotics or sedatives to ¼ to ½ of the pre-'Thorazine' level.

Obstetrics – *Intramuscular dose* in labor and delivery is 12.5 mg. to 25 mg. (0.5-1 cc.), administered when dilation of the cervix reaches 3 to 5 centimeters or when strong labor is established. At the same time (but not mixed in the syringe with 'Thorazine'), ¼ to ½ the usual dose of a narcotic or sedative and, if desired, 0.4 mg. of scopolamine may be administered. Depending upon blood pressure, respiration and the general condition of the patient, the initial 'Thorazine' dose (alone or with reduced amounts of the other agents) may be repeated in 3 to 5 hours if necessary.

Surgery (Adults) – ***Preoperatively,*** *oral dose* is 25 mg. to 50 mg., 2 to 3 hours before the operation. *Intramuscular dose* is 12.5 mg. to 25 mg. (0.5-1 cc.), 1 to 2 hours before the operation. ***During surgery*** 'Thorazine' should be administered only if needed to control nausea and vomiting, retching, hiccups, or other acute symptoms. *Intramuscular dose* is 12.5 mg. (0.5 cc.), repeated in ½ hour if necessary and if no hypotension occurs.

Intravenous dose should be no more than 2 mg. per fractional injection, with injections at not less than 2-minute intervals. Also, it should not exceed 25 mg. 'Thorazine' should be diluted to 1 mg./cc. (1 cc. mixed with 24 cc. of physiologic saline solution). ***Postoperatively,*** *oral dosage* is 10 mg. to 25 mg. q4-6h, p.r.n. *Intramuscular dosage* is 12.5 mg. to 25 mg. (0.5-1 cc.), repeated in one hour if necessary and if no hypotension occurs.

PEDIATRIC DOSAGE AND ADMINISTRATION

Nausea and Vomiting, Behavior Disorders and Pain – *Oral dosage* is on the basis of ¼ mg./lb. of body weight q4-6h, until symptoms are controlled (i.e., for 40 lb. child—10 mg. q4-6h). Calculate 'Thorazine' Syrup dosage at 10 mg./5 cc. tsp. *Rectal dosage* is on the basis of ½ mg./lb. of body weight q6-8h, p.r.n. (i.e., for 20-30 lb. child—half of a 25 mg. suppository q6-8h). *Intramuscular dosage* is on the basis of ¼ mg./lb. of body weight q6-8h, p.r.n. In children up to 5 years (or 50 lbs.)—not over 40 mg./day. In children 5-12 years (or 50-100 lbs.)—not over 75 mg./day.

Pain—Because 'Thorazine' potentiates the action of narcotics and sedatives, reduce the dosage of these agents to ¼ to ½ of the pre-'Thorazine' level.

Behavior Disorders—In severe cases, 50-100 mg. daily has been used and, in older children, 200 mg. or more daily may be required.

Surgery (Children) – ***Preoperatively,*** dose is on the basis of ¼ mg./lb. of body weight given either orally 2 to 3 hours before the operation, or intramuscularly 1 to 2 hours before. ***During surgery,*** the dose is on the basis of ⅛ mg./lb. of body weight, repeated in ½ hour if necessary and if no hypotension occurs. The intravenous dose should be no more than 1 mg. per fractional injection, with injections at not less than 2-minute intervals. Intravenous dosage during surgery should not exceed recommended intramuscular dosage and should always be diluted to 1 mg./cc. ***Postoperatively,*** dosage is on the basis of ¼ mg./lb. of body weight, either orally q4-6h, p.r.n., or intramuscularly, a single dose repeated in one hour if necessary and if no hypotension occurs.

NOTES ON PARENTERAL ADMINISTRATION

Except for acute ambulatory cases, parenteral administration should generally be reserved for bedfast patients. Parenteral administration should always be made with the patient lying down and remaining so for at least ½ hour afterward because of possible hypotensive effects. The injection should be given *slowly, deep* into the upper outer quadrant of the buttock. If irritation and pain at the site of injection are problems, dilution of 'Thorazine' Injection with physiologic saline solution or 2% procaine solution may be helpful. Subcutaneous administration is not advisable, and care should be taken to avoid injecting undiluted 'Thorazine' Injection into a vein. Intravenous administration is recommended only for severe hiccups and surgery.

Because contact dermatitis has been reported, avoid getting the solution on hands or clothing.

SIDE EFFECTS

The drowsiness caused by 'Thorazine' may be unwanted in some patients. It is usually mild to moderate and disappears after the first or second week of therapy. If, however, drowsiness is troublesome, it can usually be controlled by lowering the dosage or by administering small amounts of dextro amphetamine.

Other side effects that have been reported occasionally are dryness of the mouth, nasal congestion, some constipation, miosis in a few patients and, very rarely, mydriasis. Mild fever (99°F.) may occur occasionally during the first days of therapy with large intramuscular doses. During 'Thorazine' therapy some patients have an increased appetite and gain weight. Usually these patients reach a plateau beyond which they do not gain further weight.

CAUTIONS

Jaundice: In the more than 14 million patients who have been treated with 'Thorazine' in the United States, the incidence of jaundice—regardless of indication, dosage, or mode of administration—has been low. Few cases have occurred in less than one week or after six weeks. Jaundice due to 'Thorazine' is of the so-called "obstructive" type; is without parenchymal damage; and is usually promptly reversible upon the withdrawal of 'Thorazine'. Because detailed liver function tests of 'Thorazine'-induced jaundice give a picture which mimics extrahepatic obstruction, exploratory laparotomy should be withheld until sufficient studies confirm extrahepatic obstruction.

Agranulocytosis: Agranulocytosis, although rare, has been reported in patients on 'Thorazine' therapy. Patients receiving 'Thorazine' should be observed regularly and asked to report at once the sudden appearance of sore throat or other signs of infection. If white blood counts and differential smears give an indication of cellular depression, the drug should be discontinued, and antibiotic and other suitable therapy should be instituted. Because most reported cases have occurred between the fourth and the tenth weeks of treatment, patients on prolonged therapy should be observed particularly during that period.

A moderate suppression of total white blood cells is sometimes observed in patients on 'Thorazine' therapy. If not accompanied by other symptoms, it is not an indication for discontinuing 'Thorazine'.

Potentiation: 'Thorazine' prolongs and intensifies the action of many central nervous system depressants, such as barbiturates and narcotics. Consequently, it is advisable to stop administration of such depressants before initiating 'Thorazine' therapy. Later the depressant agents may be reinstated, starting with low doses, and increasing according to response. Approximately ¼ to ½ the usual dosage of such agents is required when they are given in combination with 'Thorazine'. (However, 'Thorazine' does not potentiate the anticonvulsant action of barbiturates. In patients who are receiving anticonvulsants, the dosage of these agents—including barbiturates—should not be reduced if 'Thorazine' is started. Rather, 'Thorazine' should be started at a very low dosage and increased, if necessary.)

Hypotensive Effect: Postural hypotension and simple tachycardia may be noted in some patients. In these patients, momentary fainting and some dizziness are characteristic and usually occur shortly after the first parenteral dose, occasionally after a subsequent parenteral dose—very rarely after the first oral dose. In most cases, prompt recovery is spontaneous and all symptoms disappear within ½ to 2 hours with no subsequent ill effects. Occasionally, however, this hypotensive effect may be more severe and prolonged, producing a shock-like condition. In consideration of possible hypotensive effects, the patient should be kept under observation (preferably lying down) for some time after the initial parenteral dose. If, on rare occasions, hypotension does occur, it can ordinarily be controlled by placing the patient in a recumbent position with head lowered and legs raised. If it is desirable to administer a vasoconstrictor, 'Levophed' and 'Neo-Synephrine'★ are the most suitable. Other pressor agents, including epinephrine, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents and cause a further lowering of blood pressure.

Antiemetic Effect: The physician should always bear in mind that the antiemetic effect of 'Thorazine' may mask signs of overdosage of toxic drugs and may obscure diagnosis of conditions such as intestinal obstruction and brain tumor.

Dermatological Reactions: Dermatological reactions have been reported. Most have been of a mild urticarial type, suggesting allergic origin. Some of them appear to be due to photosensitivity, and it is advisable that patients on 'Thorazine' avoid undue exposure to the summer sun.

Neuromuscular Reactions: With very large doses of 'Thorazine', as frequently used in psychiatric cases over long periods, there have been a few patients who have exhibited neuromuscu-

★'Levophed' and 'Neo-Synephrine' are the trademarks (Reg. U.S. Pat. Off.) of Winthrop Laboratories for its brands of levarterenol and phenylephrine respectively.

lar reactions (extrapyramidal symptoms) which closely resemble parkinsonism. Such symptoms are reversible and usually disappear within a short time after the dosage has been decreased or the drug withdrawn. These neuromuscular reactions can also be controlled by the concomitant administration of standard anti-parkinsonism agents.

Lactation: Moderate engorgement of the breast with lactation has been observed in female patients receiving very large doses of 'Thorazine'. This, however, is a transitory condition which disappears on reduction of dosage or withdrawal of the drug.

CONTRAINDICATIONS

In comatose states due to central nervous system depressants (alcohol, barbiturates, narcotics, etc.), and also in patients under the influence of large amounts of barbiturates or narcotics.

AVAILABLE

Tablets, 10 mg., 25 mg., 50 mg. and 100 mg., in bottles of 50, 500 and 5000; 200 mg., for use in mental hospitals, in bottles of 500 and 5000. (Each tablet contains chlorpromazine hydrochloride, 10 mg., 25 mg., 50 mg., 100 mg., or 200 mg.)

Ampuls, 1 cc. and 2 cc. (25 mg./cc.), in boxes of 6, 100 and 500. (Each cc. contains, in aqueous solution, chlorpromazine hydrochloride, 25 mg.; ascorbic acid, 2 mg.; sodium bisulfite, 1 mg.; sodium sulfite, 1 mg.; sodium chloride, 6 mg.)

Multiple-dose Vials, 10 cc. (25 mg./cc.), in boxes of 1, 20 and 100. (Each cc. contains, in aqueous solution, chlorpromazine hydrochloride, 25 mg.; ascorbic acid, 2 mg.; sodium bisulfite, 1 mg.; sodium sulfite, 1 mg.; sodium chloride, 1 mg. Contains benzyl alcohol, 2%, as preservative).

Spansule® capsules, 30 mg., 75 mg., 150 mg. and 200 mg., in bottles of 30, 250 and 1500; also 300 mg., in bottles of 30 and 1500. (Each 'Spansule' capsule contains chlorpromazine hydrochloride, 30 mg., 75 mg., 150 mg., 200 mg., or 300 mg.)

Syrup, 10 mg./teaspoonful (5 cc.), in 4 fl. oz. bottles. (Each 5 cc. contains chlorpromazine hydrochloride, 10 mg.)

Suppositories, 25 mg. and 100 mg., in boxes of 6. (Each suppository contains chlorpromazine, 25 mg. or 100 mg.; glycerin, glyceryl monopalmitate, glyceryl monostereate, hydrogenated cocoanut oil fatty acids, hydrogenated palm kernel oil fatty acids, lecithin.)

Concentrate (for hospital use), 30 mg./cc., in 4 fl. oz. bottles, packages of 12 and 36; and in 1 gal. bottles. (Each cc. contains chlorpromazine hydrochloride, 30 mg.)

Prescribing information adopted January, 1961

COMPAZINE®

brand of prochlorperazine

PRESCRIBING INFORMATION

Antiemetic • Tranquilizer

'Compazine' provides a beneficial calming effect and prompt antiemetic action with unusual freedom from drowsiness and depressing effect. Clinical experience in several million patients has shown 'Compazine' to be promptly effective in low dosage, with minimal side effects in the dosage range recommended for everyday practice.

INDICATIONS

1. ***Anxiety, tension, agitation,*** confusion, chronic alcoholism and behavior disorders in children.

2. ***Emotional stress associated with somatic conditions*** such as g.i. disorders, cardiovascular conditions, hypertension, menopause, premenstrual tension, neurodermatitis, arthritis, asthma, cancer, tuberculosis and tension headache.

3. ***Nausea and vomiting of widely varying causes*** such as pregnancy, postoperative conditions, viral gastroenteritis and other infectious conditions, irradiation therapy and motion sickness. In most patients, relief is provided within a short time after one oral dose.

4. ***In surgery and obstetrics*** to prevent or control: (a) nausea, vomiting and retching; and (b) fear, tension and restlessness.

5. ***In psychiatry*** to control agitation, anxiety, tension and confusion that may be seen in psychotic states.

ADMINISTRATION AND USUAL DOSAGE

Dosage should be determined according to the severity of the condition and the response of the patient. It is important to begin therapy with the lowest recommended dosage. In hospitalized patients or those under adequate supervision, higher doses may be indicated.

USUAL ADULT DOSAGE

Tablets: The usual starting dosage is 5 mg. three or four times daily. Some patients will respond better when subsequent dosage is raised to 10 mg. t.i.d. or q.i.d. Dosage over 40 mg. daily should be used only in resistant cases.

Spansule® sustained release capsules: The usual starting dosage is one 15 mg. 'Spansule' capsule taken upon arising, or one 10 mg. 'Spansule' capsule in the morning and evening. Some patients may subsequently require dosage increased to one 30 mg. capsule in the morning. Dosage over 40 mg. daily should be used only in resistant cases. (B.i.d. dosage of the 30 mg. capsule should be limited to severe cases.)

Dosage recommendations for other oral forms of 'Compazine' may be applied to 'Compazine' *Spansule* capsules on the basis of the total daily dose in milligrams. (For example: one 15 mg. 'Compazine' *Spansule* capsule replaces 5 mg. 'Compazine' Tablets, t.i.d.) All strengths have the same *duration* of action. They differ only in *intensity* of therapeutic effect.

In "morning sickness" of pregnancy, one 'Compazine' *Spansule* capsule taken before retiring affords antiemetic activity throughout the night and into the morning, thus protecting against "morning sickness."

The 15 mg. 'Compazine' *Spansule* capsule is ideal for once-a-day administration. The 10 mg. 'Compazine' *Spansule* capsule is ideal for twice-a-day (q12h) administration.

Syrup: 5 mg. to 10 mg. (1 to 2 teaspoonfuls) three or four times daily.

Suppositories: Usual dosage in adults is one 25 mg. 'Compazine' Suppository twice daily.

Injection: Total parenteral dosage in 24 hours should not exceed 40 mg.

For intramuscular administration, an initial dose of 5 mg. to 10 mg. (1 to 2 cc.) of 'Compazine' Injection should be injected *deeply* into the upper outer quadrant of the buttock. Repeat, if necessary, at intervals of 3 to 4 hours. Pain at the site of injection has not been a problem. ***For intravenous administration,*** see surgery section. Dilution is not required. ***Subcutaneous administration*** is not advisable because of local irritation.

It is recommended that 'Compazine' Injection not be mixed with other agents in the syringe.

Dermatitis due to contact with 'Compazine' has not been a problem. However, it is recommended that nurses or others giving frequent injections take precautions to avoid getting the solution on their hands or clothing.

'Compazine' Injection should be protected from light, since exposure may cause discoloration. Slight yellowish discoloration will not significantly alter the potency or therapeutic efficacy. However, if markedly discolored, the solution should be discarded.

IN SURGERY (Adults)

ROUTE	DOSAGE
preoperatively	
Intramuscular injection	5 mg. to 10 mg. (1-2 cc.)

1 to 2 hours before induction of anesthesia. Repeat once in 30 minutes if necessary.

ROUTE	DOSAGE
Intravenous injection	5 mg. to 10 mg. (1-2 cc.)

15 to 30 minutes before induction of anesthesia.

Intravenous infusion	20 mg. (4 cc.) per liter of isotonic solution

Add to I.V. infusion 15 to 30 minutes before induction. Repeat once if necessary.

during surgery

Intramuscular or Intravenous injection	5 mg. to 10 mg. (1-2 cc.)

When needed to control acute symptoms. Repeat once if necessary.

postoperatively

To prevent anxiety, nausea, vomiting, or emergence excitement, add to I.V. infusion: 20 mg. (4 cc.) per liter of isotonic solution.

For immediate control of acute nausea, vomiting, retching, or emergence excitement, inject 5 mg. to 10 mg. (1-2 cc.), I.V. or I.M. Repeat once if necessary.

IN OBSTETRICS

'Compazine' dosage should be adjusted to the individual patient and her condition in accordance with the general use of the drug (i.e., 5 mg. to 10 mg. per dose; 15 mg. to 40 mg. per day). The following dosage suggestions should prove satisfactory for the majority of obstetric patients.

To relieve anxiety or prevent vomiting during the first stage of labor, the usual dosage is 10 mg. of 'Compazine' by intramuscular injection. As labor progresses, or if it is prolonged, subsequent 10 mg. doses may be administered as needed. The total daily dose need rarely exceed 30 mg.

To control postpartum anxiety or nausea and vomiting, the usual total daily dose of 'Compazine' is 15 mg. to 30 mg. administered orally or intramuscularly.

NOTE: 'Compazine' has no clinically significant potentiating effect on narcotics, anesthetics, or sedatives. However, because the 'Compazine' patient is calm and relaxed, it is sometimes possible to produce satisfactory analgesia with less than the customary amounts of these agents. This lack of potentiating effect also minimizes the risk of intensifying or prolonging the effect of residual anesthetics and other depressant agents used in surgery or labor and delivery.

As with intravenous administration of any surgical or obstetric adjuvant, the increased possibility of hypotension should be kept in mind if 'Compazine' is administered by either intravenous injection or infusion.

USUAL CHILDREN'S DOSAGE

It is important always to use the lowest effective dosage, because as dosage is raised the possibility of side effects increases. There have been occasional cases of neuromuscular reactions (extrapyramidal symptoms) in children. These have been transitory and reversible.

Nausea and vomiting are usually controlled during the first day of therapy. Therefore more than one day's therapy is seldom necessary.

Weight	Dosage	Not to exceed
Under 20 lbs.	not recommended	
20-29 lbs.	2.5 mg. once or twice a day	7.5 mg. per day
30-39 lbs.	2.5 mg. b.i.d. or t.i.d.	10.0 mg. per day
40-85 lbs.	2.5 mg. t.i.d. or 5 mg. b.i.d.	15.0 mg. per day

For behavior disorders, dosage may be increased gradually, if necessary, within the following daily limits:

2 to 6 years of age: Total daily dose should not exceed 20 mg.
6 to 12 years of age: Total daily dose should not exceed 25 mg.

For rapid control of nausea and vomiting or behavior disorders:

Injection: For children under 12 years of age, each dose should be calculated on the basis of 0.06 mg. of 'Compazine' per pound of body weight and should be administered by deep intramuscular injection. For example, a 40-pound child would receive an injection of 2.5 mg. (0.5 cc.). Control is usually obtained with a single dose.

'COMPAZINE' IN PSYCHIATRY

'Compazine' is indicated for control of agitation, anxiety, tension and confusion that may be seen in such conditions as schizophrenias; manic-depressive states, manic phase; severe personality disorders; involutional psychoses; degenerative conditions; and senile psychoses.

ADULTS

Oral psychiatric dosage: *In relatively mild conditions,* as may be seen in private psychiatric practice or on outpatient clinics, the suggested starting dosage is 5 mg. t.i.d. or q.i.d. Some patients will respond better when subsequent dosage is raised to 10 mg. t.i.d. or q.i.d. *In moderate or severe conditions,* when patients are either hospitalized or under adequate supervision, the suggested starting dosage is 10 mg. t.i.d. or q.i.d. Dosage should be increased gradually until symptoms are controlled or side effects become bothersome. Experience has shown that when dosage is increased gradually (by small increments every two or three days) side effects either do not occur or are easily controlled.

Some patients will obtain satisfactory results on 50 mg. to 75 mg. of 'Compazine' daily. In more severe disturbances, the optimum dosage in most patients is 100 mg. to 150 mg. daily. With oral administration, response ordinarily becomes evident within a day or two. Longer periods of treatment are usually required before maximal improvement is obtained.

I.M. psychiatric dosage: For immediate control of severely disturbed adult patients, an initial dose of 10 mg. to 20 mg. (2-4 cc.) should be injected deeply into the upper outer quadrant of the buttock. If necessary, this dose should be repeated every 2 to 4 hours to gain control of the patient. Patients often respond shortly after the first injection. In resistant cases, the initial dose may be repeated hourly. More than three or four doses are seldom necessary. If, in rare cases, parenteral medication is indicated over a prolonged period, 10 mg. to 20 mg. (2-4 cc.) at 4- to 6-hour intervals is the usual dosage. Pain and irritation at the site of injection have rarely been encountered and some patients have been given the drug intramuscularly for periods of several weeks. After control is achieved by intramuscular administration, most patients can be switched to an oral form of the drug at the same dosage level or higher.

CHILDREN *(2 to 12 years)*

Oral psychiatric dosage: The suggested children's starting dosage in psychiatry is 2.5 mg. (½ teaspoonful of syrup) two or three times daily, or 5 mg. (one teaspoonful of syrup or one 5 mg. tablet) twice daily, according to body weight. During the first day, the total daily dose should not exceed 10 mg. Dosage is then increased according to the patient's response. (2.5 mg. and 5 mg. suppositories are also available.)

For ages 2 to 6, the total daily dosage usually does not exceed 20 mg. *For ages 6 to 12,* the total daily dosage usually does not exceed 25 mg. Because extrapyramidal symptoms have been reported in children as well as in adults, it is important to use the lowest effective dosage.

SIDE EFFECTS

In the dosage range recommended for everyday practice, side effects have been infrequent, transitory and usually mild. A few patients may experience a mild drowsiness when first taking 'Compazine'. There may also be occasional cases of dizziness,

skin reaction and neuromuscular reactions (extrapyramidal symptoms); rarely, hypotension.

Neuromuscular Reactions

Occasionally, neuromuscular reactions (extrapyramidal symptoms) have been observed with 'Compazine' therapy. It is important, therefore, to use the lowest effective dosage, because as dosage is raised the possibility of these reactions increases.

Motor Restlessness: A few patients on 'Compazine'—particularly those in whom dosage has been raised to higher levels—may experience a transient unpleasant stimulation or jitteriness, characterized by restlessness and insomnia. The dosage of 'Compazine' should not be increased while these side effects are present. Patients should be reassured that such effects are temporary and will disappear spontaneously. In those cases where the symptoms are particularly bothersome, reduction of dosage or the concomitant administration of a sedative may be helpful.

Dystonias: These neuromuscular reactions are seen in a significant percentage of hospitalized mental patients on high dosages. The muscles of the face and shoulder girdle may be selectively involved. Symptoms observed have included spasm of the neck muscles, extensor rigidity of back muscles, carpopedal spasm, eyes rolled back, trismus and swallowing difficulty. Despite some similarity to symptoms of serious neurologic disorders, these reactions are usually promptly reversible by temporary discontinuance of 'Compazine' therapy and administration of a sedative such as phenobarbital. The dosage and route of administration should be determined according to the severity of the symptoms. Patients should be reassured that the symptoms are transitory. Depending on the severity of the dystonia, suitable supportive measures, such as maintaining a clear airway and adequate hydration, should be employed. Note: It has been reported that injectable administration of Benadryl* may also be helpful.

Pseudo-parkinsonism: These neuromuscular reactions may resemble the classic parkinsonism syndrome. Treatment should include temporary discontinuance of 'Compazine' therapy and the administration of any standard anti-parkinsonism agent (see *PDR*). Patients should also be reassured that these symptoms are transitory. Depending on the severity of symptoms, suitable supportive measures, such as maintaining a clear airway and adequate hydration, should be employed.

CAUTIONS

Clinical experience has demonstrated that 'Compazine', a phenothiazine derivative, has a wide margin of safety and that there is little likelihood of blood or liver toxicity. The physician should be aware, however, of their possible occurrence.

The antiemetic action of 'Compazine' may mask signs of overdosage of toxic drugs or may obscure the diagnosis of conditions such as intestinal obstruction and brain tumor.

'Compazine' has no clinically significant potentiating action. However, if depressant agents are used in conjunction with this drug, the possibility of an additive effect should be kept in mind.

CONTRAINDICATIONS

'Compazine' is contraindicated in comatose or greatly depressed states due to central nervous system depressants.

AVAILABLE

There is a dosage form of 'Compazine' for every medical need. **Tablets,** 5 mg. and 10 mg. and, for use in psychiatry, 25 mg., in bottles of 50, 500 and 5000. Each tablet contains 5 mg., 10 mg., or 25 mg. of prochlorperazine as the dimaleate.

'Spansule' capsules, 10 mg., 15 mg. and 30 mg., in bottles of 30, 250 and 1500; and, for use in psychiatry, 75 mg., in bottles of 30 and 1500. Each capsule contains 10 mg., 15 mg., 30 mg., or 75 mg. of prochlorperazine as the dimaleate.

Ampuls, 2 cc. (5 mg./cc.), in boxes of 6, 100 and 500. Each cc. contains, in aqueous solution: 5 mg. prochlorperazine as the ethanedisulfonate, 1 mg. sodium sulfite, 1 mg. sodium bisulfite, 8 mg. sodium phosphate and 12 mg. sodium biphosphate.

Multiple-dose Vials, 10 cc. (5 mg./cc.), in boxes of 1, 20 and 100. Each cc. contains, in aqueous solution: 5 mg. prochlorperazine as the ethanedisulfonate, 5 mg. sodium biphosphate, 12 mg. sodium tartrate, 0.9 mg. of sodium saccharin and 0.75% benzyl alcohol as preservative.

Suppositories, 2½ mg. (for young children), 5 mg. (for older children) and 25 mg. (for adults), in boxes of 6. Each suppository contains: 2½ mg., 5 mg., or 25 mg. of prochlorperazine with glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated cocoanut oil fatty acids, hydrogenated palm kernel oil fatty acids and lecithin.

Syrup, 5 mg./teaspoonful (5 cc.), in 4 fl. oz. bottles. Each 5 cc. contains 5 mg. of prochlorperazine as the ethanedisulfonate.

Concentrate (for hospital use), 10 mg./cc. in 4 fl. oz. bottles, cartons of 12 and 36. Each cc. contains 10 mg. of prochlorperazine as the ethanedisulfonate.

Prescribing information also available in *Compazine® Reference Manual, Physicians' Desk Reference,* or from your SK&F representative or your pharmacist.

Prescribing information adopted January 1961.

*Trademark Reg. U.S. Pat. Off.: 'Benadryl' for diphenhydramine hydrochloride, Parke-Davis.

STELAZINE®

brand of trifluoperazine

PRESCRIBING INFORMATION

INDICATIONS

In general practice and in psychiatry 'Stelazine' is outstanding among tranquilizers because it relieves anxiety, agitation and tension—without sedation. Nor does it cause euphoria. 'Stelazine' is also effective in relieving anxiety either accompanying or causing somatic conditions. Where anorexia and insomnia are problems, 'Stelazine' usually produces a marked improvement in appetite and sleep patterns.

'Stelazine' provides a fast therapeutic response. On a convenient b.i.d. dosage regimen, many patients who have failed to respond to other agents, or have responded only poorly, are promptly relieved of their symptoms. With symptoms allayed, rapport with the physician is facilitated, and patients are more receptive to counselling or psychotherapy.

In hospitalized psychiatric patients 'Stelazine' produces rapid response in many diagnostic categories. These include acute and chronic schizophrenias, manic-depressive psychoses, involutional psychoses, chronic brain syndrome and mental deficiency.

'Stelazine' can combat psychotic symptoms without causing drowsiness. It can quiet hyperactive patients and activate withdrawn patients, and it has a marked beneficial effect on delusions and hallucinations.

'Stelazine' can rapidly terminate acute psychotic episodes. On the admissions service, intensive 'Stelazine' therapy often results in early discharges.

Also noteworthy is the effectiveness of 'Stelazine' in the treatment of hard-core, chronic and refractory schizophrenics. When administered to a group of such patients, it characteristically produces significant improvement in at least 30% to 40% of them.

ADMINISTRATION AND DOSAGE

Dosage of 'Stelazine' should be adjusted to the needs of the individual.

1. Adult Dosage for Use in Everyday Practice

The recommended dosage is 1 mg. or 2 mg. twice daily. In everyday practice, optimal results are usually achieved within this range, so that it is seldom necessary to exceed 4 mg. daily.

Because of the inherent long action of 'Stelazine', patients may be controlled on convenient b.i.d. administration; some patients may be maintained on once-a-day administration.

2. Adult Dosage for Use in Psychiatric Practice

oral (for office patients and outpatients with anxiety): The usual starting dosage is 1 mg. or 2 mg. b.i.d. In the treatment of these patients, it is seldom necessary to exceed 4 mg. a day. (Some patients with more severe disturbances, and discharged mental patients, may require higher dosages.) In some patients, maintenance dosage can be reduced to once-a-day administration.

oral (for patients who are either hospitalized or under adequate supervision): The usual starting dosage is 2 mg. to 5 mg. b.i.d. (Small or emaciated patients should always be started on the lower dosage.)

The majority of patients will show optimum response on 15 mg. or 20 mg. daily, although a few may require 40 mg. a day or more. It is important to give doses that are high enough for long enough periods of time – especially in chronic patients.

Optimum therapeutic dosage levels should be reached within two or three weeks after the start of therapy. When maximum therapeutic response is achieved, dosage may be reduced gradually to a satisfactory maintenance level.

intramuscular (for prompt control of severe symptoms): The usual dosage is 1 mg. to 2 mg. (½-1 cc.) by deep intramuscular injection q4-6h, p.r.n. More than 6 mg. within 24 hours is rarely necessary. As soon as a satisfactory response is observed, oral medication should be substituted at the same dosage level or slightly higher.

Only in very exceptional cases should intramuscular dosage exceed 10 mg. within 24 hours. Since 'Stelazine' has a relatively long duration of action, injections should not be given at intervals of less than 4 hours because of the possibility of an excessive cumulative effect.

'Stelazine' Injection has been exceptionally well tolerated; there is little, if any, pain and irritation at the site of injection.

3. Dosage for Psychotic and Mentally Defective Children

The dosages given below apply to children, ages 6 to 12, who are either hospitalized or under adequate supervision.

oral: The starting dosage is 1 mg. administered once a day or b.i.d., depending on the size of the child. Dosage may be increased gradually until symptoms are controlled or until side effects become troublesome. Both the rate and the amount of dosage increases should be carefully adjusted to the size of the child and the severity of the symptoms, and the lowest effective dosage should always be used. Once control is achieved, it is usually possible to reduce dosage to a satisfactory maintenance level.

In most cases, it is not necessary to exceed 15 mg. of 'Stelazine' daily. However, some older children with severe symptoms may require, and be able to tolerate, higher dosages.

intramuscular: There has been little experience with the use of 'Stelazine' Injection in children. However, if it is necessary to achieve rapid control of severe symptoms, 1 mg. (½ cc.) of 'Stelazine' may be administered intramuscularly once or twice a day, depending on the size of the child. Once control is achieved, usually after the first day, the oral dosage forms of 'Stelazine' should be substituted for the Injection.

SIDE EFFECTS

In the dosage range of 2-4 mg. daily, side effects from 'Stelazine' are infrequent. When they do occur, they are usually slight and transitory. Mild drowsiness occurs in a small percentage of patients; this usually disappears after a day or two of 'Stelazine' therapy. There are occasional cases of dizziness, mild skin reaction, dry mouth, insomnia and fatigue; rarely, neuromuscular (extrapyramidal) reactions.

In hospitalized psychiatric patients receiving daily 'Stelazine' dosages of 10 mg. or more, clinical experience has shown that, when side effects occur, their appearance is usually restricted to the first two or three weeks of therapy. After this initial period, they appear infrequently, even in the course of prolonged therapy. Termination of 'Stelazine' therapy because of side effects is rarely necessary.

Side effects observed include dizziness, muscular weakness, extrapyramidal symptoms, anorexia, rash, lactation and blurred vision. Drowsiness has occurred, but has been transient, usually disappearing in a day or two.

Neuromuscular (Extrapyramidal) Reactions

These symptoms are seen in a significant number of hospitalized mental patients receiving 'Stelazine'. They may be characterized by motor restlessness, be of the dystonic type, or they may resemble parkinsonism.

motor restlessness: Some patients may experience an initial transient period of stimulation or jitteriness, chiefly characterized by motor restlessness and sometimes insomnia. These patients should be reassured that this effect is temporary and will disappear spontaneously. The dosage of 'Stelazine' should not be increased while these side effects are present.

If this turbulent phase becomes too troublesome, the symptoms can be controlled by a reduction of dosage or the concomitant administration of a barbiturate.

dystonias: These symptoms are rare outside of mental hospitals, but they may be observed occasionally in patients who have received 'Stelazine' as a mild tranquilizer.

Symptoms may include: spasm of the neck muscles, sometimes progressing to torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crisis and protrusion of the tongue.

The onset of the dystonias may be sudden. A primary characteristic of these symptoms is their intermittency. They may last several minutes, disappear and then recur. There is typically no loss of consciousness and definite prodromata are usually present. Initially, these intermittent symptoms occur in a crescendo of intensity. Then as the effect of the drug wears off, the intervals between the occurrence of symptoms become longer, and the intensity of the symptoms subsides.

Despite their similarity to symptoms of serious neurological disorders, these dystonias are usually promptly reversible and need not cause undue alarm. They usually subside gradually within a few hours, and almost always within 24 to 48 hours, after the drug has been temporarily discontinued. If 'Stelazine' therapy is discontinued, it should be reinstituted at a lower dosage.

Treatment is symptomatic and conservative. *In mild cases,* reassurance of the patient is often sufficient therapy. Barbiturates are also useful. *In moderate cases,* barbiturates will usually bring rapid relief. The dosage and route of administration of the barbiturate used should be determined by the intensity of the symptoms and the response of the patient. *In more severe adult cases,* the administration of an anti-parkinsonism agent (see *Physicians' Desk Reference)* produces rapid, often dramatic, reversal of symptoms. Also, intravenous caffeine and sodium benzoate seems to be an effective and rapid antagonist to the dystonias. Depending on the severity of the dystonia, suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed. *In children,* reassurance and barbiturates will usually control symptoms. Dosage and route of administration should be determined according to the intensity of symptoms and response of patient.

Note: It has been reported that injectable administration of 'Benadryl' may also be helpful in controlling dystonias.

pseudo-parkinsonism: These symptoms are extremely rare outside of mental hospitals.

Symptoms include: mask-like facies; drooling; tremors; pill-rolling motion; and shuffling gait.

Reassurance and sedation are important components of effective therapy. In the majority of cases these symptoms are readily reversible when an anti-parkinsonism agent is administered concomitantly with 'Stelazine'. Occasionally it is necessary to lower the dosage or to temporarily discontinue the drug. Depending on the severity of symptoms, suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed. If 'Stelazine' therapy is discontinued, it should be reinstituted at a lower dosage.

CAUTIONS

Clinical experience has demonstrated that 'Stelazine', a phenothiazine derivative, has a wide range of safety and that there is little likelihood of either blood or liver toxicity. The physician should be aware, however, of their possible occurrence.

One of the results of 'Stelazine' therapy may be an increase in mental and physical activity. In some patients, this effect may not be desired. For example, although 'Stelazine' has relieved anxiety and, at the same time, anginal pain in patients with angina pectoris, a few such patients have complained of increased pain while taking 'Stelazine'. Therefore, if 'Stelazine' is used in angina patients, they should be observed carefully and, if an unfavorable response is noted, the drug should be withdrawn.

Hypotension has not been a problem, but nevertheless adequate precautions should be taken when the drug is used in patients with impaired cardiovascular systems.

The antiemetic action of 'Stelazine' may mask signs of overdosage of toxic drugs or may obscure the diagnosis of conditions such as intestinal obstruction and brain tumor.

Although 'Stelazine' has shown very little potentiating activity, caution should be observed when it is used in large doses in conjunction with sedatives or depressants.

CONTRAINDICATIONS

'Stelazine' is contraindicated in comatose or greatly depressed states due to central nervous system depressants.

AVAILABLE

Tablets, 1 mg. and 2 mg., in bottles of 50, 500 and 5000. (Each tablet contains 1 mg. or 2 mg. of trifluoperazine as the dihydrochloride.)

For psychiatric patients who are hospitalized or under close supervision:

Tablets, 5 mg. and 10 mg., in bottles of 50, 1500 and 5000. (Each tablet contains 5 mg. or 10 mg. of trifluoperazine as the dihydrochloride.)

Multiple-dose Vials, 10 cc. (2 mg./cc.), in boxes of 1 and 20. (Each cc. contains, in aqueous solution, 2 mg. of trifluoperazine as the dihydrochloride, 4.75 mg. of sodium tartrate, 11.6 mg. of sodium biphosphate, 0.3 mg. of sodium saccharin, and 0.75% of benzyl alcohol as preservative.)

Concentrate (for hospital use), 10 mg./cc., in 2 fl. oz. bottles, in cartons of 4 and 12. (Each cc. contains 10 mg. of trifluoperazine as the dihydrochloride.)

Prescribing information adopted July 1961

PARNATE®

brand of tranylcypromine

PRESCRIBING INFORMATION

The physician should be familiar with the material on dosage, side effects and cautions given below before prescribing 'Parnate', and with the principles of monoamine oxidase inhibitor therapy and the side effects of this class of drugs as reported in the literature. Also, the physician should be familiar with the symptomatology of mental depressions and alternative methods of treatment to aid in the careful selection of patients for 'Parnate' therapy.

INDICATIONS AND LIMITATIONS OF USE

'Parnate' is indicated for the relief of symptoms of mental depression which may include dejected mood, self-depreciation, lowered activity levels, difficulty in making decisions, disturbed eating and sleeping patterns, and variations of these basic symptoms as described in the literature. The therapeutic utility of monoamine oxidase inhibitors is limited specifically to depressive symptoms; these drugs may aggravate some co-existing symptoms such as agitation or anxiety.

In psychiatry, 'Parnate' is indicated in the following diagnostic categories, subject to the limitation stated above: reactive and other psychoneurotic depressions, involutional melancholia, depressive phase of manic-depressive psychosis, psychotic depressive reactions. In the psychiatric treatment of severe endogenous depressions, it is impossible to predict, with presently known data, which patients will respond best to 'Parnate' and which to ECT. 'Parnate' may be indicated in some reactive depressions in which ECT is not indicated. 'Parnate' is not recommended to treat essentially normal responses to temporary situational difficulties.

Note: In depressed patients, the possibility of suicide should always be considered and adequate precautions taken. Exclusive reliance on drug therapy to prevent suicidal attempts is unwarranted, as there may be a delay in the onset of therapeutic effect or an increase in anxiety and agitation. Also, of course, some patients fail to respond to drug therapy.

CLINICAL EXPERIENCE

Extensive clinical trials with 'Parnate' have confirmed its effectiveness and versatility. As always in the evaluation of drugs for psychic disorders, some variation in efficacy has been reported.

These studies provide the following data on the effectiveness and fundamental properties of 'Parnate':

1. In 500 patients on whom complete data are available for statistical analysis, marked or moderate improvement was reported in 77% of the nonpsychotic patients. Marked improvement was reported in 40% and moderate improvement in 27% of the psychotic patients. Some investigators have pointed out that improvement in certain instances, particularly in milder cases, may have been due to spontaneous remission of symptoms.
2. Improvement is seen within 48 hours to three weeks after starting 'Parnate'; the response can be accelerated by using higher than standard initial dosages.
3. 'Parnate' acts primarily as an antidepressant rather than as a euphoriant. Patients feel essentially normal on 'Parnate' therapy.
4. 'Parnate' can facilitate psychotherapy by increasing the patient's willingness to exert mental effort and reducing symptom-centered preoccupations.
5. 'Parnate' appears to prevent relapses in some patients who have been treated initially with ECT.

DOSAGE

Dosage should be adjusted to the requirements of the individual patient. Dosage increases should be made only in increments of 10 mg. per day and ordinarily at intervals of one to three weeks. Side effects occur more often as dosage is increased.

Reduction from peak to maintenance dosage may be desirable before withdrawal. If withdrawn prematurely, original symptoms will recur. No tendency to produce rebound depressions of greater intensity has been seen with 'Parnate', although this is a theoretical possibility in patients treated at high dosages. Experimental work indicates that inhibition of monoamine

oxidase persists for only a few days after withdrawal. Thus, any side effects due to this inhibition will probably recede rapidly upon withdrawal, which should be a distinct advantage of 'Parnate' therapy when the patient exhibits poor tolerance to antidepressant medication.

Because there is a striking relationship between dosage and speed of response, two dosage schedules are provided:

A. Standard dosage. (This schedule will not always produce prompt results, but it will hold the incidence of side effects to a minimum.)

1. Recommended starting dosage is 20 mg. per day – administered 10 mg. b.i.d. (morning and afternoon).
2. Continue this dosage for two to three weeks.
3. If no signs of a response appear, increase dosage to 30 mg. daily–20 mg. upon arising and 10 mg. in the afternoon.
4. Continue this dosage for at least a week.
5. As soon as a satisfactory response is obtained, dosage may usually be reduced to a maintenance level.
6. Some patients will be maintained on 20 mg. per day; many will need only 10 mg. daily.
7. If dosages above 30 mg. daily are desired for use in exceptionally resistant cases, refer to the schedule of intensive dosage.

B. Intensive dosage (for accelerated response). (This schedule is for use in hospitalized patients or those under comparable supervision whenever a prompt effect is more desirable than a relative absence of side effects.)

1. Recommended starting dosage is 30 mg. per day. Administer 20 mg. in the morning and 10 mg. in the afternoon.
2. Continue this dosage for one week.
3. If no signs of a response appear, increase dosage gradually at intervals of several days to one week.
4. Dosages above 60 mg. per day are not advisable.
5. As soon as a satisfactory response is obtained, dosage may usually be reduced gradually to a maintenance level.
6. Some patients may be maintained on 20 mg. per day; many will need only 10 mg. daily.

Note: When ECT is being administered concurrently, 10 mg. b.i.d. can usually be given during the series, then reduced to 10 mg. daily for maintenance therapy.

SIDE EFFECTS

A. At standard dosages. Side effects in patients treated with standard doses of 'Parnate' are qualitatively the same as seen at higher dosages but are generally less frequent and less severe.

The patient may experience restlessness, overstimulation, or insomnia; may notice some weakness, drowsiness, episodes of dizziness, or dry mouth; or may report nausea, diarrhea, abdominal pain, or constipation. Occasionally, headaches have occurred. Symptoms of postural hypotension have been seen most commonly, but not exclusively, in patients with pre-existent hypertension; blood pressure returns to pretreatment levels rapidly upon discontinuation of the drug. Other side effects which might occur in rare instances are tachycardia, urinary retention, significant anorexia, skin rashes, edema, palpitations, blurred vision, tinnitus, chills, paresthesia, muscle spasm and tremors, impotence, sweating and possibly paradoxical hypertension.

Most of these side effects can usually be relieved by lowering the dosage or by giving suitable concomitant medication.

B. At intensive treatment dosages. When 'Parnate' is used for intensive treatment to control symptoms more rapidly, an increase in the incidence and severity of side effects must be anticipated.

At doses above 30 mg. daily, postural hypotension is a major side effect of 'Parnate' therapy. It affects largely the systolic readings and occurs mainly, but not exclusively, in patients with a history of hypertension. Rare instances of syncope have been seen. Dosage increases should be made more gradually in patients showing a tendency toward hypotension at the starting dose. Postural hypotension can be relieved by having the patient lie down until blood pressure returns to normal.

Other side effects which may occur are listed above under *standard dosages*. Headaches have occasionally been severe and incapacitating. Overstimulated behavior, which may include increased anxiety, agitation and manic symptoms, can be evidence of either a side effect or an excessive therapeutic action; if this occurs, reduce dosage or administer a phenothiazine tranquilizer.

CAUTIONS

Extensive clinical and laboratory work has shown that there is little likelihood of blood or liver toxicity. Since 'Parnate' is a non-hydrazine compound, it should prove to be exempt from the toxic effects on the liver thought to be due to the hydrazine moiety of some other drugs. However, severe toxic reactions have occurred with some monoamine oxidase inhibitors. Pending further clinical experience, 'Parnate' should probably not be used in patients with a history of liver disease or in those with abnormal liver function tests. Drug-induced jaundice is often difficult to differentiate from other jaundice. However, there has been sufficient clinical experience with 'Parnate' to demonstrate that, if it has any potentiality for producing jaundice, the reaction must be rare. Also, the usual precautions should be observed in patients with impaired renal function since there is a possibility of accumulative effects in such patients.

Although 'Parnate' has been used in combination with various drugs (particularly Stelazine®, brand of trifluoperazine), some monoamine oxidase inhibitors have been reported to have marked potentiating effects on certain drugs, e.g., sympathomimetics, central nervous system depressants, hypotensive agents and alcohol. Therefore, the physician should bear in mind the possibility of a lowered margin of safety when 'Parnate' is combined with potent drugs and should adjust dosage carefully. 'Parnate' should not be used in combination with imipramine. (The reaction of a patient who attempted suicide with a deliberate overdosage of 'Parnate' and imipramine was more severe than would have been predicted from the properties of either drug.)

CASES REQUIRING SPECIAL CONSIDERATION

Administer with caution to patients with recent myocardial infarction or coronary artery disease with angina of effort. Increased physical activity and, more rarely, hypotension have been reported. The pharmacologic properties of 'Parnate' suggest that it may have a capacity to suppress anginal pain that would otherwise serve as a warning sign of myocardial ischemia. When 'Parnate', like any agent which lowers blood pressure, is withdrawn from patients who tend to be hypertensive, blood pressure may again rise to undesirable levels.

When 'Parnate' is combined with a phenothiazine derivative or other compound known to affect blood pressure, elderly patients and those with cardiovascular inadequacies should be observed more closely because of the possibility of additive hypotensive effects.

In patients being transferred to 'Parnate' from another monoamine oxidase inhibitor or from imipramine, allow a medication-free interval of one week, then initiate 'Parnate' using half the normal dosage for at least the first week of therapy. Similarly, a few days should elapse between the discontinuance of 'Parnate' and the administration of another monoamine oxidase inhibitor or of imipramine.

Because the influence of 'Parnate' on the convulsive threshold is variable in animal experiments, suitable precautions should be taken if epileptic patients are treated.

AVAILABLE

Tablets, 10 mg., in bottles of 50 and 1500. (Each tablet contains 10 mg. of tranylcypromine, as the sulfate.)

Prescribing information adopted Feb. 1961.

In hay fever and other seasonal allergies . . .

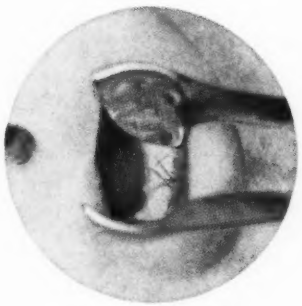
ORNADE® SPANSULE®

brand of sustained release capsules

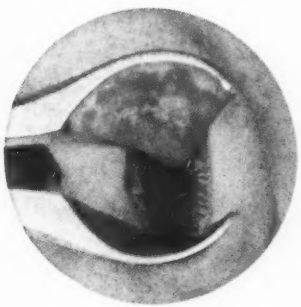
the unique oral nasal decongestant with a special drying agent

relieves sneezing—weeping—nasal congestion

for 24 hours with just two doses daily



Before taking 'Ornade'



2 hours after taking 'Ornade'

PRESCRIBING INFORMATION

The comprehensive formula of 'Ornade' *Spansule* capsules contains a special drying agent, isopropamide iodide, in addition to a decongestant and an antihistamine. Isopropamide iodide acts to reduce excessive weeping and nasal and paranasal secretions. The decongestant, phenylpropanolamine, reduces vascular engorgement and often permits blocked sinus cavities to drain. The antihistamine, 'Teldrin', reduces sneezing, rhinorrhea and itching of the eyes. Acting together, additively, these three agents combine to provide outstanding relief from upper respiratory distress.

INDICATIONS: 'Ornade' *Spansule* capsules are recommended for prompt and prolonged relief from respiratory tract congestion and hypersecretion associated with:

allergic rhinitis:
hay fever
"rose fever," etc.
the common cold
acute, subacute and chronic sinusitis
influenza
vasomotor rhinitis
postnasal drip

DOSAGE (adults and children over 6): For all-day, all-night relief, one 'Ornade' *Spansule* capsule q12h. When taken at bedtime, 'Ornade' keeps patients symptom-free throughout the night and usually enables them to wake up in the morning uncongested and with airways free.

FORMULA: Each 'Ornade' *Spansule* sustained release capsule contains 8 mg. of Teldrin® (brand of chlorpheniramine maleate) and 50 mg. of phenylpropanolamine hydrochloride, so prepared that a therapeutic dose is released immediately and the remaining medication, released slowly and without interruption, sustains the effect for 10 to 12 hours; and 2.5 mg. of isopropamide, as the iodide. Because isopropamide iodide is inherently long-acting, it has not been necessary to put it into sustained release form; therefore, the entire dose of isopropamide iodide is released upon ingestion.

SIDE EFFECTS: Drowsiness, "nervousness," or insomnia may occur on rare occasions, but are usually mild and transitory.

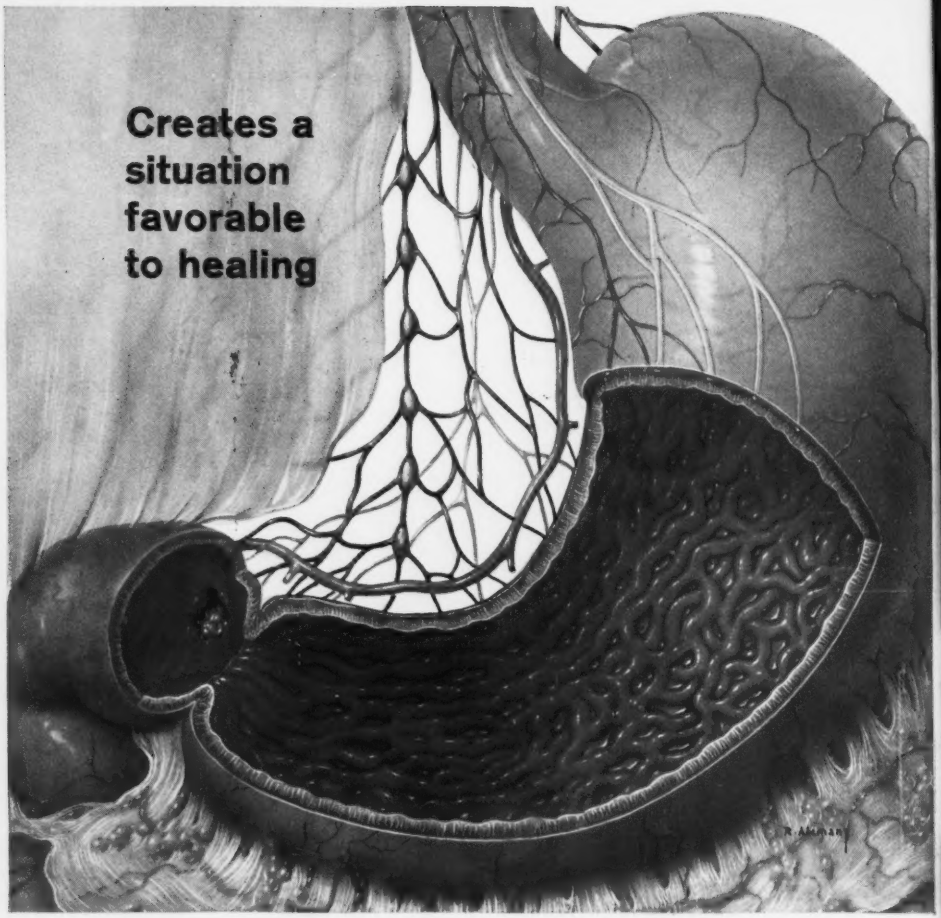
CAUTIONS AND CONTRAINDICATIONS: Use with caution in the presence of severe hypertension. 'Ornade' should not be used in patients with glaucoma or prostatic hypertrophy.

AVAILABLE: 'Ornade' *Spansule* capsules are available in bottles of 30 and 250.

Prescribing information adopted January, 1961.

Smith Kline & French Laboratories

SK&F



In ulcer: 'Combid' *Spansule* capsules provide emotional as well as physical control. 'Combid' reduces secretion, spasm and nausea—as well as anxiety, tension and apprehension—for 10 to 12 hours after just one capsule. A convenient q12h regimen provides 24-hour, continuous control; creates a situation favorable to healing.

SK&F

Combid® Spansule®

brand of sustained release capsules

'Combid' *Spansule* capsules are a logical combination of 5 mg. of Darbid® (brand of isopropamide) as the iodide, a unique, inherently long-acting anticholinergic, and 10 mg. of Compazine® (brand of prochlorperazine) as the dimaleate, the outstanding tranquilizer/antiemetic, in sustained release form.

Among the many conditions in which 'Combid' *Spansule* capsules are indicated are: peptic ulcer, hyperchlorhydria, pyloroduodenal irritability, irritable or spastic colon, gastric neurosis, gastritis, aerophagia, pyrosis, "nervous stomach," functional diarrhea, drug-induced diarrhea, mucous colitis, ulcerative colitis, genitourinary spasm, and nausea and vomiting of pregnancy.

DOSAGE: One 'Combid' *Spansule* capsule b.i.d. (every 12 hours). Some patients may require only one capsule every 24 hours, on arising. Only in the exceptional patient will it be necessary to increase the dosage to two capsules b.i.d. (morning and evening).

CAUTIONS AND CONTRAINDICATIONS: As is true with any preparation containing an anticholinergic, 'Combid' *Spansule* capsules should not be prescribed for patients with glaucoma, pyloric obstruction, or prostatic hypertrophy. Also, because of the antiemetic action of the 'Compazine' component (a phenothiazine derivative), 'Combid' *Spansule* capsules should not be used where nausea and vomiting are believed to be a manifestation of intestinal obstruction or brain tumor.

Clinical experience has demonstrated that 'Combid' has a wide margin of safety and that there is little likelihood of blood or liver toxicity or neuromuscular reactions (extrapyramidal symptoms). The physician should be aware, however, of their possible occurrence. When 'Combid' is used with depressant drugs, the possibility of an additive effect should be borne in mind. An occasional patient may experience mild drowsiness when first taking 'Combid'.

Prescribing information adopted January, 1961.